HOMERUS or the clinical significance of self-measurement of blood pressure

Citation for published version (APA):

Verberk, W. J. (2006). *HOMERUS or the clinical significance of self-measurement of blood pressure*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht.
<https://doi.org/10.26481/dis.20060623wv>

Document status and date:
Published: 01/01/2006

DOI:
[10.26481/dis.20060623wv](https://doi.org/10.26481/dis.20060623wv)

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

HOMERUS or the clinical significance of
self-measurement of blood pressure

© Willem Verberk, Maastricht 2006

ISBN-10: 90-5278-531-7

ISBN-13: 978-90-5278-531-8

Cover design: Anita Verberk-Jansen

Layout: Tiny Wouters

Production: Datawyse | Universitaire Pers Maastricht

HOMERUS or the clinical significance of self-measurement of blood pressure

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 23 juni 2006 om 12.00 uur

door

Willem Verberk

Promotor:

Prof. dr. P.W. de Leeuw

Co-promotor:

Dr. A.A. Kroon

Beoordelingscommissie:

Prof. dr. C.P. van Schayck (voorzitter)

Prof. dr. J.W. van Ree

Prof. dr. J.L. Severens

Prof. dr. J.A. Staessen, University of Leuven, Belgium

Prof. dr. G.S. Stergiou, Third University Department of Medicine,
Athens, Greece

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door steun van de Nederlandse Hartstichting.

Aan Anita
Aan mijn ouders

Contents

Chapter 1	General introduction	9
Chapter 2	Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study. Rationale and study design of the HOMERUS-trial	15
Chapter 3	Comparison of randomisation techniques for clinical trials with data from the HOMERUS-trial	31
Chapter 4	Self-measurement of blood pressure at home reduces the number of anti-hypertensive drugs: results of the HOMERUS-trial	47
Chapter 5	The optimal scheme of self blood pressure measurement as determined from ambulatory blood pressure recordings	67
Chapter 6	Masked hypertension is not a discrete entity but a result of the moment	81
Chapter 7	Masked hypertension, a review of the literature	95
Chapter 8	The white coat effect does not change with multiple measurement visits	109
Chapter 9	Home blood pressure measurement, a systematic review	123
Chapter 10	General discussion	143
	Samenvatting	155
	Dankwoord	165
	Curriculum vitae	171

Chapter 1

Introduction to the thesis

Introduction to the thesis

Hypertension is a highly important risk factor for cardiovascular diseases, such as cerebrovascular accident, ischemic heart disease, cardiac and renal failure. Approximately 25-30% of the general population suffers from this condition and after the age of 70 even 60-70%¹. This makes it essential to diagnose the disorder in an early stage in order to provide optimal treatment. The latter is particularly important in patients for whom target blood pressure has recently been lowered, e.g. those with co-morbid states, like diabetes mellitus and renal disease². Therefore, next to accurately measuring blood pressure, it is becoming increasingly important to be able to detect small differences of blood pressure. Although, from a technical point of view precise measurement of blood pressure is feasible, detection of hypertension still remains a problematic issue due to the generally adopted inexactness of this measurement during daily clinical practise.

For decades, the gold standard for clinical blood pressure measurement has been the one taken by a trained health care provider using a mercury sphygmomanometer and applying the Korotkoff sounds, an auscultatory technique that was introduced in 1905³. However, there is increasing evidence that this procedure often leads to misclassification of individuals as hypertensive. There are several reasons that can lead to a wrong diagnosis, of which some are avoidable and others not. Inaccuracies in the methods encompass wrong cuff size, wrongly placed cuff, wrong sitting position (crossed legs, arm not at the heart level, etcetera). Therefore, blood pressure measurement should be performed meticulously, according to well-described guidelines⁴. Further, the auscultatory method highly depends on hearing, reaction speed and digit preference of the observer⁵. The latter would plea for the use of automatic devices. Most of such devices are based on the oscillometric principle. This technique, introduced in 1969 by Posey *et al.*⁶, determines the mean arterial blood pressure from which the systolic and diastolic blood pressure are derived by algorithm.

The unavoidable problems of conventional blood pressure measurements are related to the variability of blood pressure⁷. Due to momentary fluctuations, blood pressure values can strongly deviate from the daily average value at the time of the measurements. Another cause for bias is the white coat effect, a tendency for blood pressure to increase in the presence of a physician⁸. Currently, a rather new phenomenon has been discovered, of which it is still uncertain whether it is caused by the patient's inherent variability in blood pressure or that it represents a clinical entity. This phenomenon is the so-called masked hypertension: a blood pressure that is low at the time of (office) measurement but elevated elsewhere⁹.

Since an abnormal blood pressure at the time of measurement can have severe consequences for a patient, accurate performed measurements are highly essential. At the moment, the most reliable tool for unbiased determinations is ambulatory blood pressure measurement (ABPM). It is superior to conventional office blood pressure in predicting cardiac, renal and cerebrovascular damage^{10,11}. In addition, ABPM has the advantage that it can reproduce the diurnal variation and the short-term variability of blood pressure. Both factors have proven to be highly predictive representative for the development of cardiovascular morbidity^{12,13}. However, since ABPM devices are expensive, uncomfortable for the patient and require a technician, they are not available for every patient. In addition, ABPM is not highly reproducible on frequent measurements. Therefore, a good alternative has been found in the assessment of self-measurements of blood pressure at home.

Despite the fact that the benefits of self-measurement of blood pressure have been known for a long time and several authoritative bodies^{14,15} recommend self-measurement next to conventional blood pressure measurement, little research has been done as to its clinical usefulness¹⁶. Therefore, the Home versus Office MEasurements: Reduction of Unnecessary treatment Study (HOMERUS) was developed in order to investigate in a multicentre, randomised design whether self-measurement of blood pressure at home is a reliable tool to base antihypertensive treatment on and whether self-measurements lead to a decrease in antihypertensive drug prescriptions. In the present thesis, studies related to the clinical utility of self-measurement of blood pressure, as assessed in HOMERUS, have been described.

Outline of the thesis

In chapter 2 the HOMERUS study protocol has been described. The baseline characteristics of the study population and the main results are shown in chapter 3 and 4, respectively. In order to determine the number of measurements necessary for a reliable estimate of a patient's true blood pressure, we developed an optimal measurement scheme, which is written in chapter 5. Additionally, in chapter 6 we investigated the frequency and reproducibility of masked hypertension, chapter 7 is a review of the current literature on masked hypertension. The prevalence and reproducibility of the white coat effect and white coat hypertension is described in chapter 8. Chapter 9 provides a state of the art paper of home blood pressure measurement and finally in chapter 10 the results of these studies are summarised and discussed.

References

1. Staessen JA, Wang J, Bianchi G, Birkenhager WH. Essential hypertension. *Lancet* 2003;361:1629-41.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.
3. Koroktoff N. On the subject of methods of measuring blood pressure. *Bull Imp Military Med Scad St Petersburg* 1905;11:365-7.
4. Myers MG. Blood pressure measurement and the guidelines: a proposed new algorithm for the diagnosis of hypertension. *Blood Press Monit* 2004;9:283-6.
5. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
6. Posey JA, Geddes LA, Williams H, Moore AG. The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure. *Cardiovasc Res Cent Bull* 1969;8:15-25.
7. Pickering TG. Variability of blood pressure. *Blood Press Monit* 1998;3:141-5.
8. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Gattobigio R, Sacchi N, Porcellati C. White coat hypertension and white coat effect. Similarities and differences. *Am J Hypertens* 1995;8:790-8.
9. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002;40:795-6.
10. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801.
11. Mancia G, Frattola A, Ulian L, Santucci C, Parati G. Blood pressures other than the one at the clinic. *Blood Press Suppl* 1997;2:81-5.
12. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, Lonati L, Magrini F, Zanchetti A. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004;22:273-80.
13. Cicconetti P, Morelli S, Ottaviani L, Chiarotti F, De Serra C, De Marzio P, Costarella M, Sgreccia A, Ciotti V, Marigliano V. Blunted nocturnal fall in blood pressure and left ventricular mass in elderly individuals with recently diagnosed isolated systolic hypertension. *Am J Hypertens* 2003;16:900-5.
14. Kjeldsen SE, Erdine S, Farsang C, Sleight P, Mancia G. 1999 WHO/ISH Hypertension Guidelines -highlights & ESH Update. *Blood Press* 2003;12:181-2.
15. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328:634-40.
16. Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G, O'Brien ET. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA* 2004;291:955-64.

Chapter 2

Home versus Office blood pressure

MEasurements: Reduction of Unnecessary
treatment Study. Rationale and study design of
the HOMERUS-trial

WJ Verberk, AA Kroon, AGH Kessels, C Dirksen, PJ Nelemans, JWM Lenders,
Th Thien, GA van Montfrans, AJ Smit, PW de Leeuw

Blood Press 2003;12:326-33

Abstract

The Home versus Office MEasurements, Reduction of Unnecessary treatment Study (HOMERUS) is a multicentre prospective study, primarily designed to examine in subjects with mild to moderate hypertension whether treatment decisions based on home blood pressure measurements can lead to reduction in the use of antihypertensive drugs and the associated costs, compared to office blood pressure measurements. After inclusion, 360 patients are randomised to two groups. In one group, antihypertensive therapy is based on blood pressure measured in the outpatient clinic: the office pressure (OP) group. In the other group, antihypertensive therapy is based on home blood pressure measurements: the self pressure (SP) group. All readings, both in OP and in SP, are obtained with the same validated oscillometric device, the Omron HEM-705CP. Treatment decisions are taken by an independent physician at the coordinating centre, who is unaware whether the patient belongs to the SP or OP group. Following a standardised treatment schedule, blood pressure is targeted at 120 to 139 mmHg for systolic and 80 to 89 mmHg for diastolic pressure. Patients are followed for one year. At the start and at the end of the study, ambulatory blood pressure measurements are obtained as a reference. Microalbuminuria and echocardiography are assessed to evaluate the possible development of target organ damage. It is expected that, at the end of the trial, patients in both groups will have the same blood pressure, at the expense of more medication in the OP group. Therefore, a cost-minimisation analysis will be performed first. If short-term effects appear not to be comparable for OP and SP, a cost-effectiveness analysis will be performed to assess the value of the SP strategy in comparison to standard practice. In addition, medication compliance is recorded within random subgroups of the SP and OP groups by means of Medication Event Monitoring System (MEMS) V TrackCaps.

Introduction

Despite its inherent sources of error, conventional sphygmomanometry is still the most widely used method to measure blood pressure¹. However, it can easily lead to the white coat effect, which may be present in as much as one-fifth of hypertensive patients². In such patients blood pressure is remarkably lower in the absence of the observer and in extreme cases may even be normal outside the doctor's office^{3,4}. Especially in the latter case this may lead to an artifactual diagnosis of hypertension (white coat hypertension).

Ambulatory blood pressure monitoring (ABPM) has the great advantage of obtaining multiple readings without the interference of an observer. Although this technique has rapidly gained acceptance^{5,6} it will be difficult to implement it in primary care, and it will certainly not be available to every hypertensive patient. Therefore, cheaper and easier solutions are necessary, from which every patient can benefit.

Self-measurement of blood pressure may be a suitable and less costly alternative for ABPM⁷⁻⁹. With this method, it is possible to collect multiple readings without being bothered by the white coat effect¹⁰⁻¹². In addition, self-measurements may enhance compliance to prescribed drugs^{13,14} and reduce the number of clinic visits¹⁵⁻¹⁷. Thus, the implementation of self-measurements in the routine diagnostic and therapeutic follow-up of hypertensives may be a cost-effective procedure¹⁸. An obvious disadvantage of self-measurements is that patients tend to report lower blood pressure values than what was actually measured¹⁹. This may make it necessary to use monitors with a memory device, which can store a number of blood pressure readings for later assessment.

Recently, a large-scale study to address the clinical significance of self-measurement of blood pressure was carried out by Staessen *et al.*²⁰. In this study two groups were compared, in which both office and self measured blood pressure data are obtained. However, because both groups measured their blood pressure at home, any positive effect of self-measurements may have diluted the difference between the two groups. For example, patients belonging to the SP group may be inclined to decrease compliance with treatment if their blood pressure measured at home turns out to be lower compared to office blood pressure measurement. This makes good comparison of compliance impossible between the groups. In addition, due to differences between the Dutch and Belgium Healthcare System, the results of this study cannot be simply extrapolated to The Netherlands.

Therefore, the objective of the present study is to examine whether decisions concerning antihypertensive therapy based on home blood pressure measurements can lead to reduction in the use of antihypertensive drugs and the associated costs in subjects with mild to moderate hypertension, when

compared to decisions based on office blood pressure measurements. In addition, we will investigate whether home blood pressure measurements increase compliance with medication as assessed by means of Medication Event Monitoring System (MEMS) V TrackCaps within random subgroups of the SP and OP groups.

Study design

The Home versus Office MEasurements, Reduction of Unnecessary treatment Study (HOMERUS) is a multi-centre, prospective, randomised, study with a parallel-group design. The primary outcome variable in this study is the amount of antihypertensive drugs used and the associated costs. To this end, a cost-minimisation analysis (see economic evaluation) will be performed. In case there are differences in blood pressures between the self pressure (SP) and office pressure (OP) group, a cost-effectiveness analysis will be done. Secondary objectives include the assessment of the percentage of patients with refractory hypertension, the degree of target organ damage, the degree of compliance to treatment, side-effects of treatment, Quality of Life (QoL), and the estimation of societal costs.

Patients

Patients are recruited from the outpatient departments of the participating hospitals and from general practices surrounding these centres. Both previously treated and untreated patients with essential hypertension qualify for inclusion. When this is safe, previous medication will be discontinued and study medication will be withheld during a 1-month run-in period. The inclusion and exclusion criteria are listed below.

Inclusion criteria

- I. Males and females aged 18 years and above.
- II. Average blood pressure between 139 and 200 mmHg for systolic or between 90 and 120 mmHg for diastolic blood pressure.
- III. Participating subjects are physically and mentally able to measure their own blood pressure.
- IV. Subjects are willing to remain in follow-up during a period of one year.
- V. Signed informed consent.

Exclusion criteria

- I. The presence of clinically manifest cardiovascular events (angina pectoris, heart failure, hypertensive encephalopathy, or prior myocardial infarction or cerebrovascular accident).

- II. Severe non-cardiovascular disease (e.g. malignancy), which will interfere with adequate follow-up.
- III. Allergy or contra-indications for the antihypertensive drugs used in this study.
- IV. Serum creatinine above 150 $\mu\text{mol/l}$.
- V. Clinically significant orthostatic hypotension (a drop in systolic blood pressure of more than 20 mmHg upon standing).

Blood pressure devices

For blood pressure measurements at home and in the physician's office, the Omron HEM-705CP automated blood pressure monitor with printer is used. The Omron HEM-705CP achieved an overall B/A grading according to the British Hypertension Society (BHS) system and fulfilled the accuracy criteria of the Association for the Advancement of Medical Instrumentation (AAMI)²¹. The ambulatory blood pressure measurements that are used as reference are carried out with a Spacelabs 90217-1B automatic device.

Blood pressure measurement

At each visit, blood pressure is measured three times in sitting position after 5 min of rest with an interval of 2 min. The three measurements are averaged for analysis. Ambulatory blood pressure measurement (ABPM) was performed for 26-h. Blood pressure readings were obtained at 15-min intervals from 07.00 h to 23.00 h and at 30-min intervals during the remainder of the day. Home blood pressure measurements are recorded during the week preceding the next visit. Recordings are performed for seven consecutive days in the morning and in the evening, with each session consisting of three readings in sitting position. Patients are asked to register their blood pressure readings on special case record forms and to print out the results. Home blood pressure is defined as the mean of all home measurements obtained from the patient. For all types of measurement the same cuff size is used. Standard cuffs have a 24 x 14 cm inflatable bladder. If arm circumference exceeds 31 cm, larger cuffs with a bladder size of 32 x 15 cm were used.

Participating centres

The following centres participate in this study: University Hospital Maastricht (coordinating centre), University Medical Centre Groningen, Academic Medical Centre Amsterdam University, Radboud University Nijmegen, Medical Centre, and 11 general practices surrounding these hospitals.

Overall study design

Initial visit. The patient's eligibility is checked, a medical history is recorded and a physical exam is performed. The follow-up is performed by a trained nurse practitioner and the patient's own medical doctor performs the blood pressure measurements in the clinic. All patients who are considered eligible for the study are requested to terminate or cut back their current antihypertensive therapy and to return after 14 days for the second visit. Laboratory measurements are obtained, including determination of serum creatinine, two 24-h urine collections to assess microalbuminuria, and an electrocardiogram (ECG). ABPM and echocardiography are scheduled to be performed within 2-3 weeks. For assessment of the QoL and cost effectiveness, the patient is asked to fill out questionnaires (see economic evaluation, subsection 5).

Second visit. If the blood pressure remains between predetermined (139/89 mmHg and 200/120 mmHg) ranges, patients will be randomly allocated to the SP group or to the OP group. When the patient is randomised to the SP group, he or she is instructed by the nurse to measure blood pressure with the home blood pressure device (Omron HEM-705CP).

Third visit. Patients start with the first step of active medication (see treatment schedule) if their blood pressure is still above 139/89 mmHg. All patients will have clinic blood pressure measurements but treatment for the SP group is based on the mean of the home measurements. The patient is instructed not to communicate with his/her medical doctor what kind of blood pressure method is used for treatment decisions.

Follow-up. After the third visit, patients are followed up monthly for blood pressure measurements. Drug treatment is adjusted according to the treatment schedule, either based on SP or OP measurements. At visit 5, additional laboratory analyses are performed, i.e. serum creatinine measurements and (optional) 24-h urinary collections for the assessment of microalbuminuria. At several visits, the patients are asked to fill out questionnaires. After visit 5, patients are followed up at 2-months intervals. At the last visit of the study, patients undergo the same laboratory assessments as have been performed at the beginning of the study: serum creatinine, microalbuminuria, ECG, ABPM, and echocardiography.

Treatment schedule

At each follow-up visit, the achieved blood pressure level has to be evaluated and, if necessary, treatment will be adjusted. In both groups, the goal blood pressure ranges between 120 and 139 mmHg systolic and between 80 and 89 mmHg diastolic (average of three readings in sitting position). In patients who are above the target blood pressure (systolic >139 mmHg and/or diastolic >89 mmHg), antihypertensive treatment will be intensified by one step. If blood

pressure is lower than the target (systolic <120 mmHg and diastolic <80 mmHg), treatment will be reduced by one step. In some cases, this may lead to temporarily termination of treatment. If patients are on their target, treatment remains unchanged. For patients who have severe hypertension at the start of the study (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg), extra visits will be performed in order to accelerate the treatment schedule. In case of refractory hypertension, defined as a sitting blood pressure exceeding 160 mmHg systolic or 100 mmHg diastolic while the patient is already on maximum combination therapy, additional strategies from other drug classes are instituted in order to further decrease blood pressure level. The percentage of patients with refractory hypertension will be one of the secondary outcome variables.

Should the patient develop signs of cardiovascular complications at any point (including symptoms indicative of ischemia, such as transient ischemic attacks or angina pectoris), the patient will be withdrawn from the study; he or she will receive appropriate treatment and will be supervised in open follow-up. In addition, as a matter of safety, the patient will be withdrawn from the study if at three consecutive visits, the mean office-measured blood pressure level exceeds 200 mmHg systolic or 120 mmHg diastolic.

Patients who are withdrawn from the study will still be required to complete follow-up (including ABPM at the end of the study), in order to enable an intention-to-treat analysis (see statistical considerations).

All patients receive lifestyle recommendations, which are reinforced at each visit by a nurse. Pharmacological treatment is blinded for the patient and the physician but not for the research nurse. In order to keep the number of pills constant during the first three treatment steps, placebo tablets were added to Lisinopril. Treatment will, therefore, be instituted stepwise according to the following schedule (see also Figure 2.1):

- I) Step 1: Lisinopril 10 mg once daily plus one tablet of placebo once daily;
- II) Step 2: Lisinopril 20 mg once daily plus one tablet of placebo once daily;
- III) Step 3: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg;
- IV) Step 4: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg plus amlodipine 5 mg.

In patients in whom an angiotensin-converting enzyme inhibitor is contraindicated, lisinopril 10 mg and 20 mg will be replaced by atenolol 50 mg and 100 mg, respectively.

Figure 2.1 HOMERUS treatment schedule and main assessments during the 1-year follow-up. For the OP group, treatment decisions are based on the average of three office blood pressure measurements. For the SP group, treatment decisions are based on the mean home blood pressure measurements.

Ethics

Informed consent, in accordance with the declaration of Helsinki, has been obtained from all patients prior to entering the study. Good clinical practice is maintained and the study protocol has been approved by the ethical committees of all participating centres before inclusion of patients into the study.

Economic evaluation

1. *Cost-minimisation analysis.* In principle, a cost-minimisation analysis will be performed from the societal perspective, since blood pressure levels are not expected to differ between the OP and SP group. However, “blood pressure” is an intermediate endpoint, and it is not certain whether (long-term) QoL, morbidity and mortality are actually comparable for OP and SP. When short-term results regarding blood pressure level, QoL, morbidity and mortality turn out to be similar in OP and SP, a cost-minimisation approach will be followed. If the above conditions for cost-minimisation analysis are not fulfilled, a cost-effectiveness analysis (incremental cost per

quality-adjusted life year, QALY) will be performed. A QALY is a generic outcome in which life expectancy is adjusted by the QoL outcome (on a scale of 0 to 1), i.e. utility value.

2. *Cost-effectiveness analysis and decision analysis.* A cost-effectiveness analysis (also from the societal perspective) will be performed when the following results apply:
 - i. Blood pressure levels between OP and SP are different, i.e. the difference in systolic pressure is larger than 5 mmHg and/or the difference in diastolic pressure is larger than 3 mmHg.
 - ii. QoL, morbidity and mortality between OP and SP are different, which are related to the difference in blood pressure between OP and SP and/or to other factors, amongst which the use of antihypertensive medication.

Short-term differences between OP and SP as listed above may also have future consequences regarding cardiovascular morbidity and mortality. In this case, the final ABPM values will be entered in a 10-year decision analytic Markov model, in order to perform a long-term cost-effectiveness analysis. Short-term empirical (QoL) utility results, as well as long-term QoL, possible future cardiovascular events, and survival data based on literature findings, will be used in order to determine the incremental cost-effectiveness ratio. The cost-effectiveness analysis will be expressed as the cost per QALY. Sensitivity analyses will subsequently be performed on several variables. For future costs and effectiveness data, a discount rate of 4% will be handled.

3. *Hospital costs.* Hospital costs include the costs of the outpatient department visits, antihypertensive drugs, ECGs, echocardiography, costs incurred by target organ damage, etc. Such information will be collected for each patient for one year following randomisation. In principle, costs will be obtained from the Financial Economic Department from the University Hospital of Maastricht. Costs of the other participating centres will be used if available. The hospital costs in general consist of personnel, material and capacity (equipment) costs. The indirect costs of buildings, energy, supporting departments, etcetera, will be made directly by adding them as a percentage to the direct costs according to the Dutch guidelines for cost calculations²². The costs of the self-measurement device will be calculated per patient, based on empirical data. Results will be presented as costs (cost times volume of use) and volumes of use separately, in order to make a comparison possible between the participating hospitals.
4. *Productivity losses and (health care) costs outside the hospital.* Healthcare resource use outside the hospital (additional medication, visits at the general practitioner), out-of-pocket costs to patients, and productivity losses due to sickness and disability will be determined by a cost diary,

which will be filled in three times by the patients at several predefined moments during the time of study (at the start, after one month, and at the end of the study). Productivity loss will be calculated according to the “friction cost” method. In case of household or other unpaid activities, shadow prices will be used.

5. *QoL questionnaires.* The EuroQoL-5D (EQ-5D)²³ instrument will be used every visit starting once drug treatment has been initiated, to ensure that QoL does not differ between OP and SP. The EQ-5D consists of a questionnaire, which classifies the patient into one of 243 health states (five dimensions, each with three levels) and a visual analogue scale on which patients rate their own health between 0 and 100. Furthermore, a disease-specific QoL instrument²⁴ and a general QoL instrument²⁵ will be filled in four times, at 1, 3, 7 and 12 months after the start of the study.

Compliance substudy

The effect of self-monitoring on blood pressure control and reduction of antihypertensive medication may be mediated through its effect on greater compliance with medication. To evaluate the possibility that self-measurement of blood pressure enhances adherence to medication, compliance will be recorded within random subgroups of the SP and OP groups. For this purpose, Medication Event Monitoring System (MEMS) V TrackCaps will be used. The MEMS V TrackCap is an electronic monitoring system designed to compile the dosing histories of ambulatory patients who are prescribed oral medications²⁶. Microelectronics integrated into the cap of pill containers record the time and date that the container is opened or closed. Under the assumption that the patients indeed take their medication when they open their pillboxes, MEMS V TrackCaps offer the opportunity to determine how often and at which time interval the TrackCap is opened. Since only 60 subjects per group (see statistical considerations) are necessary, this sub-study will only be performed at the coordinating centre (University Hospital Maastricht). Recordings will start once medication is introduced (visit 3) and last until the end of the study.

Statistical considerations

Patients will be randomly allocated to the SP or OP group using a dynamic minimisation procedure, taking into account the following factors: hospital or general practitioner, region, gender, age (<40 years, 40-60 years and >60 years), and (a history of) target organ damage. Randomisation is performed by a blinded person using dedicated software.

For the cost-minimisation analysis, a distribution of the costs (medication, laboratory tests, and outpatient visits) was constructed based on clinical and cost data of the Maastricht University Hospital. The mean direct costs per

patient per year of pharmacological treatment according to the medication schedule, for outpatient visits and associated laboratory tests amount to € 396.00 with a standard deviation of € 180.00. In order to become cost-saving, the costs of the self-measurement device (OMRON) of € 46.00 per year (plus costs for training) should at least be compensated. Therefore, the minimum cost reduction was set at € 92.00 per patient per year. To demonstrate such an effect with a power of 90% and a significance level (two-sided) of 0.05, the required number of patients per group is 80. However, since we aim to attain the same blood pressure in both treatment groups, it is essential that a true difference in blood pressure is not missed. To reject the hypothesis that the difference in systolic pressure is larger than 5 mmHg and/or that the difference in diastolic pressure is larger than 3 mmHg with a significance level of 5% (two-sided) and a power of 80%, 292 randomised patients are needed. To allow for a 20% dropout rate (no endpoints available) 360 patients will have to be included. In these calculations, the standard deviations of systolic and diastolic pressures were assumed to be 15 and 10 mmHg, respectively.

For the evaluation of compliance with medication, the required number of patients per group is 60, based on the following assumptions: a power of 80%, a significance level (one-sided) of <0.05 , a mean compliance rate in the OP group of 70%²⁷ and a minimal relevant difference between the SP and OP groups of 10%. The standard deviation (0.8) was estimated from a log-transformed distribution of compliance²⁶.

Data will be analysed based on the intention-to-treat principle. In relevant cases, a per-protocol analysis will be carried out as well.

Time schedule

Recruitment to HOMERUS began January 2002 and the inclusion target of 360 patients was reached in April 2003. All randomised patients are followed for a period of one year, so that the analysis of trial results can start in April 2004.

Organisation

The Steering Committee comprises one or two representatives from each participating centre. The Steering Committee is in charge of approval of the protocol and amendments, organisation, data handling, and general conduct of the study. An independent Safety and Data Monitoring Committee, comprising three members who are independent of other parts of the study, is supervising the evolution of the study, especially with respect to the occurrence of clinical events. It is also empowered to advise the Steering Committee on study termination.

Study monitors have been appointed at the coordinating centre (Maastricht) to have regular contact with the investigational sites in order to confirm

acceptability of facilities, adherence to the study protocol, accurate recording of data and to provide information and support to the investigators.

Funding

HOMERUS is an investigator driven study and is not sponsored by a pharmaceutical company. The only sponsor of this study is The Netherlands Organisation for Health, Research and Development, (grant no. 945-01-043).

Discussion

A diagnosis of hypertension should be based on accurate and repeated blood pressure measurements obtained under standardised conditions. The reference values whether to treat or not to treat hypertension are related to office blood pressure measurements and are based on long-term studies that investigated the relation between blood pressure and cardiovascular events²⁸. However, since office measurements have several disadvantages like the induction of a white coat effect², and since an increasing amount of cheap accurate automatic blood pressure devices is now available, self-measurement of blood pressure has been proposed as a suitable alternative to diagnose hypertension^{29,30}. Indeed, over the past years, this method has gained more and more acceptance. Self-measurement of blood pressure has several advantages. It eliminates the white coat effect and it offers the possibility to gather large amounts of measurements in the patient's own environment⁹⁻¹¹. Self-measurement of blood pressure is better correlated to cardiovascular mortality than office blood pressure³¹ and it may be more cost-effective by avoiding the need for frequent office visits¹⁵⁻¹⁷. Some investigators suggest that self-measurements may also improve compliance with medication^{13,14} although until now this has not been confirmed in large studies.

The present study tries to find an answer to the question whether self-measurements can be used to guide treatment decisions. In addition, we set out to explore if self-measurements improve patient's compliance compared to office measurement.

The target blood pressure level was determined according to the recommendations of the ESH guidelines that defined hypertension as a blood pressure $\geq 140/90$ mmHg³². Although there are several other reference values proposed for self-measurement of blood pressure^{32,33}, these have not yet been properly investigated. Therefore, the same reference values are used for both office and home measurements. This has the additional advantage that the physician at the coordinating centre who adjusts the treatment can be kept blinded during treatment decisions. It may be an inherent weakness of the

study that the SP group has no evidence-based target level of blood pressure, but on the other hand post-hoc analyses will allow to model the impact of self-measurements at various cut-off points of blood pressure. Previous studies have proven that during office measurements several patients show a white coat effect². This means that at that time their blood pressure is higher than in normal daily life. This makes it even possible that patients are considered hypertensive on the basis of office measurements, whereas they have a normal blood pressure in daily life: the so-called white coat hypertensives³⁴. In the normal situation, these patients unnecessarily undergo medical treatment or receive more medicines than they should. The white coat effect makes it very difficult to determine whether a patient needs medication or not. With 24-h ABPM, it is possible to get a good insight in daily blood pressure, but this is expensive, time and work consuming and uncomfortable for the patient³⁵. Therefore, self-measurement of blood pressure at home seems a good alternative. The HOMERUS-trial, in our view, could well contribute to existing knowledge by establishing whether self-measurement of blood pressure is a valid and less expensive alternative to ABPM, possibly leading to a reduction of unnecessary treatment.

References

1. Arabidze GG, Petrov VV, Staessen JA. Blood pressure by Korotkoff's auscultatory method: end of an era or bright future? *Blood Press Monit* 1996;1:321-7.
2. Pickering TG. White coat hypertension. *Curr Opin Nephrol Hypertens* 1996;5:192-8.
3. Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, Grassi G, di Rienzo M, Pedotti A, Zanchetti A. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ Res* 1983;53:96-104.
4. Verdecchia P, Schillaci G, Boldrini F, Zampi I, Porcellati C. Variability between current definitions of 'normal' ambulatory blood pressure. Implications in the assessment of white coat hypertension. *Hypertension* 1992;20:555-62.
5. Marchiando RJ, Elston MP. Automated ambulatory blood pressure monitoring: clinical utility in the family practice setting. *Am Fam Physician* 2003;67:2343-50.
6. Staessen JA, Fagard R, Thijs L, Amery A. A consensus view on the technique of ambulatory blood pressure monitoring. The Fourth International Consensus Conference on 24-Hour Ambulatory Blood Pressure Monitoring. *Hypertension* 1995;26:912-8.
7. Hond ED, Celis H, Fagard R, Keary L, Leeman M, O'Brien E, Vandenhoven G, Staessen JA. Self-measured versus ambulatory blood pressure in the diagnosis of hypertension. *J Hypertens* 2003;21:717-22.
8. O'Brien E. State of the market for devices for blood pressure measurement. *Blood Press Monit* 2001;6:281-6.
9. Stergiou GS, Voutsas AV, Achimastos AD, Mountokalakis TD. Home self-monitoring of blood pressure: is fully automated oscillometric technique as good as conventional stethoscopic technique? *Am J Hypertens* 1997;10:428-33.
10. Stergiou GS, Skeva, II, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? *J Hypertens* 1998;16:725-31.
11. Conway J. Home blood pressure recording. *Clin Exp Hypertens A* 1986;8:1247-94.
12. Fagard R, Staessen J, Thijs L. Ambulatory blood pressure during antihypertensive therapy guided by conventional pressure. *Blood Press Monit* 1996;1:279-81.
13. Vrijens B, Goetghebeur E. Comparing compliance patterns between randomized treatments. *Control Clin Trials* 1997;18:187-203.
14. Ashida T, Sugiyama T, Okuno S, Ebihara A, Fujii J. Relationship between home blood pressure measurement and medication compliance and name recognition of antihypertensive drugs. *Hypertens Res* 2000;23:21-4.
15. Wilson MD, Johnson KA. Hypertension management in managed care: the role of home blood pressure monitoring. *Blood Press Monit* 1997;2:201-6.
16. Rademaker M, Lindsay A, McLaren JA, Padfield PL. Home monitoring of blood pressure: usefulness as a predictor of persistent hypertension. *Scott Med J* 1987;32:16-9.
17. Chatellier G, Dutrey-Dupagne C, Vaur L, Zannad F, Genes N, Elkik F, Menard J. Home self blood pressure measurement in general practice. The SMART study. Self-measurement for the Assessment of the Response to Trandolapril. *Am J Hypertens* 1996;9:644-52.
18. Soghikian K, Casper SM, Fireman BH, Hunkeler EM, Hurley LB, Tekawa IS, Vogt TM. Home blood pressure monitoring. Effect on use of medical services and medical care costs. *Med Care* 1992;30:855-65.
19. Mengden T, Schwartzkopff B, Strauer BE. What is the value of home (self) blood pressure monitoring in patients with hypertensive heart disease? *Am J Hypertens* 1998;11:813-9.
20. Staessen JA, Celis H, Hond ED, Giot C, Leeman M, O'Brien E, Vandenhoven G, Fagard R. Comparison of conventional and automated blood pressure measurements: interim analysis of the THOP trial. Treatment of Hypertension According to Home or Office Blood Pressure. *Blood Press Monit* 2002;7:61-2.
21. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *PG - Blood Press Monit* 1996 Feb;1:55-61 1996:55-61.

22. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics* 2002;20:443-54.
23. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
24. Bulpitt CJ, Fletcher AE. The measurement of quality of life in hypertensive patients: a practical approach. *Br J Clin Pharmacol* 1990;30:353-64.
25. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Med Care* 1992;30:473-83.
26. Urquhart J, De Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. *Stat Med* 1998;17:251-67; discussion 387-9.
27. Stephenson J. Noncompliance may cause half of antihypertensive drug "failures". *JAMA* 1999;282:313-4.
28. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens Suppl* 1994;12:S5-14.
29. Aylett M, Marples G, Jones K. Home blood pressure monitoring: its effect on the management of hypertension in general practice. *Br J Gen Pract* 1999;49:725-8.
30. Denolle T, Waeber B, Kjeldsen S, Parati G, Wilson M, Asmar R. Self-measurement of blood pressure in clinical trials and therapeutic applications. *Blood Press Monit* 2000;5:145-9.
31. Imai Y, Hozawa A, Ohkubo T, Tsuji I, Yamaguchi J, Matsubara M, Michimata M, Hashimoto J, Fujiwara T, Nagai K, Kitaoka H, Satoh H, Hisamichi S. Predictive values of automated blood pressure measurement: what can we learn from the Japanese population - the Ohasama study. *Blood Press Monit* 2001;6:335-9.
32. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.
33. Weisser B, Mengden T, Dusing R, Vetter H, Vetter W. Normal values of blood pressure self-measurement in view of the 1999 World Health Organization-International Society of Hypertension guidelines. *Am J Hypertens* 2000;13:940-3.
34. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Zampi I, Gattobigio R, Sacchi N, Porcellati C. White coat hypertension and white coat effect. Similarities and differences. *Am J Hypertens* 1995;8:790-8.
35. Palatini P. Too much of a good thing? A critique of overemphasis on the use of ambulatory blood pressure monitoring in clinical practice. *J Hypertens* 2002;20:1917-23.

Chapter 3

Comparison of randomisation techniques for
clinical trials with data from the HOMERUS-trial

WJ Verberk, AA Kroon, AGH Kessels, PJ Nelemans, JW van Ree,
JWM Lenders, Th Thien, JC Bakx, GA van Montfrans, AJ Smit, FW Beltman,
PW de Leeuw

Blood Press 2005;14:306-14.

Abstract

Background

Several methods of randomisation are available to create comparable intervention groups in a study. In the Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study (HOMERUS), we compared the minimisation procedure with a stratified and a non-stratified method of randomisation in order to test which one is most appropriate for use in clinical hypertension trials. A second objective of this article was to describe the baseline characteristics of the HOMERUS-trial.

Methods

The HOMERUS population consisted of 459 mild-to-moderate hypertensive subjects (54% males) with a mean age of 55 years. These patients were prospectively randomised with the minimisation method to either the office pressure (OP) group, where antihypertensive treatment was based on office blood pressure (BP) values, or to the self-pressure (SP) group, where treatment was based on self-measured BP values. Minimisation was compared with two other randomisation methods, which were performed post-hoc: (i) non-stratified randomisation with four permuted blocks, and (ii) stratified randomisation with four permuted blocks and 16 strata. In addition, several factors that could influence outcome were investigated for their effect on BP by 24-h ambulatory blood pressure monitoring (ABPM).

Results

Minimisation and stratified randomisation did not lead to significant differences in 24-h ABPM values between the two treatment groups. Non-stratified randomisation resulted in a significant difference in 24-h diastolic ABPM between the groups. Factors that caused significant differences in 24-h ABPM values were: region, centre of patient recruitment, age, gender, microalbuminuria, left ventricular hypertrophy, and obesity.

Conclusion

Minimisation and stratified randomisation are appropriate methods for use in clinical trials. Many outcome factors should be taken into account for their potential influence on BP levels.

Recommendation

Due to the large number of potential outcome factors that can influence BP levels, minimisation should be the preferred method for use in clinical hypertension trials, as it has the potential to randomise more outcome factors than stratified randomisation.

Introduction

The primary purpose of randomisation in clinical trials is to create groups of patients that are similar with regard to baseline characteristics that have the potential to influence outcome. Otherwise differences in outcome at the end of a trial may be ascribed to prognostic features rather than the intervention. Therefore, randomisation is essential for good clinical practice in order to achieve an optimal balance between groups.

Randomisation can fail in two important ways. First, it can fail when an unequal number of patients is assigned to the treatment groups. Second, when the groups of patients are unbalanced for critical features that are known or suspected to affect prognosis, so-called outcome factors. In this paper, we investigated which method of randomisation is most appropriate in avoiding these potential failures. In order to attain this we compared three different methods of randomisation: the procedure of minimisation and two procedures that were performed post-hoc: non-stratified and stratified randomisation¹.

For this comparison we used data from the Home vs. Office MEasurements: Reduction of Unnecessary treatment Study (HOMERUS), a randomised clinical trial that investigated whether self-measurement of blood pressure (BP) at home is a reliable tool on which to base antihypertensive treatment².

This paper serves two purposes: the primary aim is to describe three methods of randomisation and the secondary purpose is to describe the baseline characteristics of the HOMERUS-trial.

Patients and methods

The design of the HOMERUS-trial has been described in detail elsewhere². In brief, HOMERUS is a multi-centre, prospective, randomised, double-blind trial with a parallel-group design. Patients, aged 18 years and older whose office BP was above 139 mmHg systolic and/or 89 mmHg diastolic were randomly allocated to either the self-pressure (SP) group or to the office pressure (OP) group. If randomised to the SP group, antihypertensive treatment was guided on the results of self blood pressure measurement (SBPM). In the OP group, treatment was titrated based on office blood pressure measurement (OBPM). At entry into the study, any existing antihypertensive therapy was discontinued whenever possible and patients entered a placebo run-in period of four weeks duration before study treatment was initiated. If the treating physician considered interruption of treatment to be too hazardous, the patient was switched without run-in period to the trial medication. Twenty-four-hour ambulatory blood pressure monitoring (ABPM), as a reference standard, and assessment of target organ damage (heart, kidney) took place at the end of the run-in period and at the end of the trial.

Primary aim

Minimisation.

Randomisation of patients was performed, according to the procedure of minimisation¹, by a blinded person at the coordinating centre using dedicated software. Once an eligible subject provided written informed consent the coordinator entered the subject's characteristics into a computer program, which randomised the patient.

The six outcome factors used in the randomisation process were: age (<40, 40-59 or ≥60 years), gender, centre where the patient was treated (Maastricht, Nijmegen, Amsterdam, Groningen), clinical symptoms (yes or no), type of practice of recruiting centre (general practitioner or hospital practice) and whether the patients had a placebo run-in period or not. Patients were considered to have clinical symptoms when they had a history of left ventricular hypertrophy (LVH), cardiovascular events, target organ damage of the kidney or retinopathy.

To prevent the possibility of predicting the next allocation with knowledge of characteristics from earlier patients, the probability of assignment to the treatment groups was set at 0.9 instead of 1. This means that there was a 10% chance that a patient was allocated to a treatment group different from what could be expected based on characteristics from earlier patients.

Post-hoc randomisation procedures.

In order to ascertain the adequacy of the minimisation procedure which was actually used in HOMERUS, this method was compared with two types of fixed post-hoc randomisation procedures: first, randomisation with four permuted blocks without strata (non-stratified randomisation), and second, randomisation with four permuted blocks and 16 strata (stratified randomisation)¹. The four factors used for stratified randomisation that resulted in 16 strata were: age (≤50 or >50 years), gender, clinical symptoms (yes or no) and type of practice of recruiting centre (general practitioner or hospital practice).

Outcome factors.

In order to test the influence of patient characteristics on BP levels we compared ABPM values between patients with and without some of the most common risk factors according to the European Society of Hypertension³. Comparison was performed between patients with and without LVH, obesity (BMI >30 kg/m²), microalbuminuria, hypercholesterolaemia (total cholesterol >6.5 mmol/l), increased serum creatinine level (creatinine men 115-133, women 107-124 μmol/l) and diabetes mellitus (glucose >7.0 mmol/l).

Secondary aim

Blood pressure measurement.

At each visit BP was measured three times in sitting position after 5 min of rest. The three measurements were averaged for analysis. ABPM was performed for 26 h. BP readings were obtained at 15-min intervals from 07.00 h to 23.00 h and at 30-min intervals during the remainder of the 24-h period. Readings from 09.00 h to 21.00 h and from 01.00 h to 06.00 h were used to calculate the average ABPM values. SBPMs were recorded during the week preceding the next visit. Recordings were performed for seven consecutive days in the morning and in the evening with each session consisting of three readings in sitting position.

Laboratory analyses.

Blood was drawn from fasting patients for determination of blood glucose, serum cholesterol (total and HDL-cholesterol) and serum creatinine. Two consecutive 24-h urine collections were analysed for (micro)albuminuria. Microalbuminuria was defined as an albumin concentration between 30 and 300 mg/24-h and proteinuria as an albumin concentration of 300 mg/24-h or greater³.

Echocardiography.

Two-dimensionally guided echocardiograms of the left ventricle were taken at the cordal level with the patient in the partial left decubitus position. End-diastolic left ventricular internal diameter, septal and posterior wall thickness, left ventricular total diameter were calculated from at least five consecutive heart cycles. Left ventricular mass was estimated according to Devereux & Reichek⁴ and indexed to body surface area. LVH is defined as left ventricular mass index (LVMI) exceeding 125 g/m² in men and 110 g/m² in women³. All examinations were recorded on videotape and assessed by a blinded reader.

Data and statistical analysis.

To reject the hypothesis of a systolic pressure difference larger than 5 mmHg and/or a diastolic pressure difference larger than 3 mmHg with a significance level of 5% (two-sided) and a power of 80%, 292 randomised patients were needed (standard deviations of systolic and diastolic pressures 15 and 10 mmHg). To allow for a 20% drop-out rate (no endpoints available), 360 patients had to be included. During the trial, the steering committee decided to expand the number of patients further, because of additional research to compliance with treatment.

Data are presented as mean $\pm$ standard deviation. Between-group comparisons involved the following statistical methods: one-way analysis of variance Student t-test, Mann-Whitney *U*, when not normally distributed, or chi-square for proportions. To compare variance of measurements within a group of subjects paired sample Student t-tests were done. To improve mutual comparison of OBPM, SBPM, and ABPM, the OBPM value of the third visit was used since most patients were without antihypertensive treatment at that time, and ABPM and SBPM were assessed near that visit. All statistical calculations were performed using SPSS version 12.0 (SPSS, Inc. Chigaco, Illinois). From April 2002 to October 2003 four university hospitals and surrounding general practices recruited 459 patients who were randomised to either the OP or SP group. Four weeks after randomisation, i.e. at the time when study treatment was started, 29 patients (6%) had withdrawn from the study. However, this did not lead to inequality between the randomised groups (Figure 3.1). As far as study assessments were concerned, patients who had dropped out did not differ from the remaining ones. Reasons for early termination were that patients had changed their mind about willingness to stop their current antihypertensive treatment or that they considered the visits to the hospital too cumbersome or that they thought the physical examination would be too exhausting.

Figure 3.1 Flow diagram of the Run-In phase in HOMERUS

Patient characteristics. Patient characteristics ($n=459$) are given in Table 3.1. There were no differences between the randomised groups, neither for these characteristics nor for the laboratory assessments, which were performed at 430 patients prior to visit 3 (Table 3.2).

Table 3.1 Baseline characteristics of the randomised patients for the total group, the office pressure (OP) group and the self-pressure (SP) group.

	Total, 459	OP, 230	SP, 229
Males, <i>n</i> (%)	249 (54)	126 (55)	123 (54)
Age, yr (SD)	55 ± 11	55 ± 11	55 ± 11
BMI, kg/m ²	28 ± 5	28 ± 4	28 ± 5
Obesity, BMI >30 kg/m ² , <i>n</i> (%)	112 (24)	55 (24)	57 (24)
Waist-to-hip ratio, (SD)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Smoking, <i>n</i> (%)	82 (18)	40 (17)	42 (18)
Drugs, ^a <i>n</i> (%)	321 (70)	158 (69)	163 (71)
Beta-blockers, <i>n</i> (%)	133 (29)	72 (31)	61 (27)
Diuretics, <i>n</i> (%)	131 (29)	66 (29)	65 (28)
ACE, <i>n</i> (%)	112 (24)	55 (24)	57 (25)
ARB, <i>n</i> (%)	68 (15)	32 (14)	36 (16)
Calcium channel blockers, <i>n</i> (%)	56 (12)	27 (12)	29 (13)
Alpha-blockers, <i>n</i> (%)	8 (2)	2 (1)	6 (3)
Lipid lowering drugs, <i>n</i> (%)	62 (14)	33 (14)	29 (13)
TAI, <i>n</i> (%)	37 (8)	19 (8)	18 (8)

n, number of patients; BMI, body mass index; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; TAI, thrombocyte aggregation inhibitors. Data are depicted as number of patients and percentage or as mean ± standard deviation (SD). ^a Number of patients that used antihypertensive drugs at study enrolment.

Table 3.2 Laboratory results at baseline for the total group, the office pressure (OP) group and the self-pressure (SP) group.

	Total, 430	OP, 214	SP, 216
Glucose, mmol/l (SD)	5.5 (1)	5.4 (1)	5.6 (1)
Diabetes mellitus, <i>n</i> (%)	25 (6)	17 (8)	8 (4)
Cholesterol, mmol/l (SD)	5.7 (1)	5.7 (1)	5.7 (1)
Hypercholesterolaemia, <i>n</i> (%)	80 (19)	45 (21)	35 (16)
Creatinine, µmol/l (SD)	82 (16)	82 (14)	82 (17)
Creatinine level elevated, <i>n</i> (%)	12 (3)	6 (3)	6 (3)
Microalbuminuria, <i>n</i> (%)	58 (13)	30 (14)	28 (13)
Proteinuria, <i>n</i> (%)	4 (1)	2 (1)	2 (1)
Left ventricular hypertrophy, <i>n</i> (%)	61 (14)	32 (15)	29 (13)

n, number of patients. Data are depicted as number of patients and percentage or as mean ± standard deviation (SD).

Results

Primary aim

Adequacy of randomisation. Table 3.3a shows the distribution of patients between the OP and SP group over the six pre-specified outcome factors used for minimisation. There were no differences among the factors between the

randomised groups. Tables 3.3b and 3.3c show post-hoc non-stratified and stratified randomisation, respectively, as distributed over the same factors that were used at the minimisation procedure. Although there were no significant differences in distribution between the randomised groups over the six outcome factors, the minimisation method was more balanced as compared to the other randomisation methods.

Table 3.3a Result of random allocation using the minimisation method.

Treatment group	Region				Location		Age (years)			Gender		Clinical symptoms		Run-in	
	1	2	3	4	Clinic	GP	<40	40-60	>60	M	F	Y	N	Y	N
OP (n)	101	38	46	45	157	73	23	129	78	126	104	9	221	221	9
SP (n)	99	47	43	40	156	73	22	128	79	123	106	8	221	219	10
	200	85	89	85	313	146	45	257	157	249	210	17	442	440	19

Table 3.3b Result of random allocation using the randomisation with four permuted blocks and without strata.

Treatment group	Region				Location		Age (years)			Gender		Clinical symptoms		Run-in	
	1	2	3	4	Clinic	GP	<40	40-60	>60	M	F	Y	N	Y	N
OP (n)	93	46	51	40	164	66	28	128	74	125	105	9	221	221	9
SP (n)	107	39	38	45	149	80	17	129	83	124	105	8	221	219	10
	200	85	89	85	313	146	45	257	157	249	210	17	442	440	19

Table 3.3c Result of random allocation using the randomisation with four permuted blocks and with 16 strata.

Treatment group	Region				Location		Age (years)			Gender		Clinical symptoms		Run-in	
	1	2	3	4	Clinic	GP	<40	40-60	>60	M	F	Y	N	Y	N
OP (n)	91	44	48	46	157	72	19	137	73	126	103	7	222	220	9
SP (n)	109	41	41	39	156	74	26	120	84	123	107	10	220	220	10
	200	85	89	85	313	146	45	257	157	249	210	17	442	440	19

Random allocation for six outcome factors accomplished by three different methods of randomisation. A number of 459 patients were separated into two treatment groups (SP and OP) with maintenance of distribution balance for the six outcome factors. 1, Maastricht; 2, Nijmegen; 3, Amsterdam; 4, Groningen; GP, general practitioner; M, male; F, female; Y, yes; N, no.

When looking at differences in 24-h ABPM values in relation to the outcome factors, Figure 3.2 shows that BP differed significantly among four of the six factors.

Figure 3.2 Twenty-four-hour ambulatory blood pressure measurement (ABPM) illustrated for each outcome factor that was used for the minimisation method.

*** $p < 0.001$; ** $p < 0.03$. Data are depicted as mean $\pm$ standard deviation.

Figure 3.3 illustrates 24-h ABPM values between the groups after randomising patients according to the minimisation, non-stratified randomisation and stratified randomisation, respectively. Non-stratified randomisation resulted in a significant difference for 24-h diastolic ambulatory BP.

Figure 3.4 shows that patients with LVH, microalbuminuria and obesity had different BP values as compared to patients without these characteristics.

Figure 3.3 24-h Ambulatory Blood Pressure measurements for the office pressure (OP) and self-pressure (SP) group as randomised with different randomisation procedures. * $p < 0.05$. Data are depicted as mean $\pm$ standard deviation.

Figure 3.4 Twenty-four-hour ambulatory blood pressure measurements compared for patient characteristics that could influence prognosis. No LVH, patients without left ventricular hypertrophy; LVH, patients with left ventricular hypertrophy; Malb, microalbuminuria; Hchol, hypercholesterolaemia; DM, diabetes mellitus; Hcreat, elevated creatinine level. *** $p < 0.001$; ** $p < 0.03$. Data are depicted as mean $\pm$ standard deviation.

Secondary aim

Blood pressure. Table 3.4 illustrates the office BP and heart rate measurements at enrolment and during the run-in phase, as well as the results of ABPM (assessed $\pm$ three weeks after enrolment, between the second and third visit) and SBPM (assessed seven days preceding visit 3). During the four weeks going from visit 1 to visit 3 there was a significant increase ($p < 0.001$) in OBPM values from 5 mmHg systolic and 2 mmHg diastolic. Since visit 2 was an instruction visit this was skipped for some patients in the OP group. At the time ABPM was performed, there were 430 patients in the study, of whom 18 patients (4%) refused to have ABPM since they had experienced serious discomfort during earlier measurements and six patients (1%) removed the device at night due to severe inconvenience. In the SP group 11 patients (5%) did not perform or had incorrect initial SBPMs, as they had not understood the procedure; on average 39 measurements were performed. A significant stepwise difference was observed between OBPM, SBPM and ABPM, in which SBPM took an intermediate position with regard to systolic and diastolic BP ($p < 0.001$).

At the end of the run-in period, but before study medication was started, 33 out of the 430 patients (8%) appeared to have normal OBPM according to BHS guidelines⁵ ($<140/90$ mmHg) and 31 patients (7%) were normotensive according to their 24-h ABPM ($<125/80$ mmHg). Of the 406 patients who delivered sufficient day- and night-time BP values with their ABPM, 281 (69%) could be classified as dippers (defined as a night-day SBP and DBP fall $\geq 10\%$), 146 of these (52%) belonged to the OP group. White coat hypertension (clinic BP ≥ 140 and/or 90 mmHg and 24-h BP $<125/80$ mmHg) was found in 25 patients (6%), while 16 patients (4%) had reversed white coat hypertension (clinic BP $<140/90$ mmHg and 24-h BP ≥ 125 or 80 mmHg). Overall, patients were more likely to have a systolic OBPM ≥ 140 mmHg ($n=389$, 90%) than to have a diastolic OBPM ≥ 90 mmHg ($n=332$, 77%).

Table 3.4 Office blood pressure measurement (OBPM), ambulatory blood pressure measurement (ABPM), self blood pressure measurement (SBPM) at enrolment.

	Total					OP group					SP group				
	Subjects	Systolic (mmHg)	Diastolic (mmHg)	HR (beats/min)		Subjects	Systolic (mmHg)	Diastolic (mmHg)	HR (beats/min)		Subjects	Systolic (mmHg)	Diastolic (mmHg)	HR (beats/min)	
OBPM															
1 st visit	459	161 ± 19	95 ± 10	74 ± 12		230	161 ± 21	95 ± 10	73 ± 12		229	161 ± 18	96 ± 10	74 ± 12	
2 nd visit	358	164 ± 19	97 ± 10	76 ± 13		171	165 ± 20	97 ± 10	75 ± 13		187	163 ± 18	97 ± 9	77 ± 12	
3 rd visit	430	166 ± 20	97 ± 10	77 ± 13		214	165 ± 21	98 ± 11	76 ± 13		216	166 ± 19	97 ± 10	77 ± 12	
ABPM															
mean	412	143 ± 14	88 ± 9	74 ± 9		205	142 ± 14	87 ± 9	74 ± 10		207	143 ± 14	88 ± 10	73 ± 9	
day	412	148 ± 15	93 ± 10	78 ± 11		205	148 ± 15	93 ± 10	79 ± 12		207	149 ± 15	92 ± 11	78 ± 10	
night	406	127 ± 15	76 ± 10	65 ± 9		203	126 ± 16	75 ± 11	66 ± 9		203	128 ± 15	76 ± 10	65 ± 8	

Discussion

Primary aim

Our findings show that with the minimisation and stratified randomisation method, the two groups were well matched with respect to clinical characteristics. The choice of randomising for the six factors used in this study seems to be justified by the significant differences in ambulatory BP level that were found in four of the six outcome factors. The non-stratified randomisation method should be avoided for use in clinical trials, as this resulted in a significant difference in diastolic ambulatory BP between the randomised groups.

For this study, several limitations should be taken into account; minimisation was actually performed in this study, while the other methods have been performed post-hoc. Clinical symptoms, for which patients were randomised, were only registered when the patient or the treating physician knew this. We randomised for some factors that had no influence on treatment. In the present study, 459 patients were randomised of which 412 eventually performed 24-h ABPM that was used to determine similarity between the treatment groups. It is therefore possible that differences between the treatment groups are derived from missing ABPMs, although the amount of patients that performed ABPM was similar in both groups.

The non-stratified randomisation procedure resulted in a rather balanced distribution, which is probably caused by the use of four permuted blocks. These four blocks provide an equal number of patients between the treatment groups after having randomised every four patients. After each four patients, two have randomised to the OP group and two to the SP group, which can occur in six ways: 1) OOSS, 2) OSOS, 3) OSSO, 4) SSOO, 5) SOSO, 6) SOOS. With permuted blocks of size four, the number of patients assigned to each treatment within a block can never differ by more than two.

Some authorities argue that for large trials it is unnecessary to stratify^{6,7}; however, this cannot be concluded from our results. Although there were no differences for each outcome factor separately, non-stratified randomisation eventually resulted in a difference in 24-h diastolic BP between the groups.

Stratified randomisation provided more similarity with respect to outcome factors. There are several arguments that plead for use of this method: it diminishes the occurrence of type I^{8,9} and type II¹⁰⁻¹² errors and facilitates subgroup and interim analyses¹³. The latter is related to the fact that stratified randomisation provides balance in a small population. Because of this, some authoritative bodies believe that stratified randomisation is necessary for a valid

comparison in small trials ($n < 100$)¹⁴. A disadvantage of stratified randomisation is the fact that the number of outcome factors for which can be randomised is limited. According to Therneau, stratified randomisation begins to fail when the number of factor level combinations approaches half the sample size¹⁵. If we would have randomised for six factors, as were used with the minimisation method, a number of $4 \times 2 \times 3 \times 2 \times 2 \times 2 = 192$ strata would be needed. According to Kernan *et al.* the amount of factor levels should even be smaller. Their advice is that the maximum number of strata should be less than $n / (B \times 4)$ where n =number of patients in the trial and B =the block size¹². Therefore, when many variables can affect prognosis or treatment responsiveness, minimisation seems the most appropriate method.

With minimisation, the allocation of the next participant in a trial depends (wholly or partly) on the characteristics of those participants already enrolled. The aim is that each allocation should minimise the imbalance across multiple factors¹⁶. As shown in this study and also by others¹⁷, minimisation ensures excellent balance between groups for several outcome factors, even in small trials. For this reason, minimisation should be used in hypertension trials, as there are many factors that influence BP, clearly demonstrated with the data from the HOMERUS population. The present data confirmed that age, gender, LVMI, microalbuminuria, region, centre of recruitment, and BMI influenced BP level.

In our opinion, the HOMERUS population provided an excellent opportunity to determine the most appropriate randomisation method out of three. Since BP value is the most important outcome, the treatment groups have to be similar for BP level. As shown in the present study, many outcome factors can influence BP level. Therefore, this study required well-performed randomisation for many outcome factors in order to exclude the chance of an unbalanced distribution for one factor that could influence outcome and possibly cause a type I error.

Secondary aim

Participants of the HOMERUS-trial could be characterised as middle-aged, mild to moderate hypertensives, with one or two cardiovascular risk factors. Target organ damage, i.e. either LVH or albuminuria was seen in 14% of the population. Overall the average 10-year cardiovascular risk in the patients ranged between 10 and 20% according to the ESH/ESC hypertension guidelines¹⁸. Most patients, who were included in HOMERUS, were treated with antihypertensive medication at study entrance, among which beta-blockers and diuretics were most frequently prescribed. There was a stepwise difference between OBPM, SBPM and ABPM values, in which OBPM was highest and SBPM took an intermediate position with regard to systolic and diastolic BP.

Most patients (69%) could be classified as dippers and 6% of the subjects had white coat hypertension. Furthermore, according to OBPM more patients were characterised as being hypertensive by their systolic BP than by their diastolic BP.

Conclusion

Results of this study led us to conclude that minimisation and stratified randomisation provide a balanced distribution over the outcome factors. Although the HOMERUS-trial included more than 400 participants, non-stratified randomisation led to a difference in treatment groups and, therefore, should not be used in clinical trials. Stratified randomisation may approach accuracy of the minimisation method, but has the disadvantage that the amount of outcome factors that can be randomised is limited. Since there are many factors that can influence BP level, the method of minimisation, which also allows subgroup and interim analysis, should be the preferred randomisation method in hypertension trials.

References

1. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-15.
2. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
3. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.
4. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613-8.
5. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328:634-40.
6. Meier P. Stratification in the design of a clinical trial. *Control Clin Trials* 1981;1:355-61.
7. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Introduction and design. *Br J Cancer* 1976;34:585-612.
8. Birkett NJ. Adaptive allocation in randomized controlled trials. *Control Clin Trials* 1985;6:146-55.
9. Feinstein AR, Landis JR. The role of prognostic stratification in preventing the bias permitted by random allocation of treatment. *J Chronic Dis* 1976;29:277-84.
10. Miettinen OS. Stratification by a multivariate confounder score. *Am J Epidemiol* 1976;104:609-20.
11. Grizzle JE. A note on stratifying versus complete random assignment in clinical trials. *Control Clin Trials* 1982;3:365-8.
12. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. Stratified randomization for clinical trials. *J Clin Epidemiol* 1999;52:19-26.
13. Simon R. Restricted randomization designs in clinical trials. *Biometrics* 1979;35:503-12.
14. Armitage P, Gehan EA. Statistical methods for the identification and use of prognostic factors. *Int J Cancer* 1974;13:16-36.
15. Therneau TM. How many stratification factors are "too many" to use in a randomization plan? *Control Clin Trials* 1993;14:98-108.
16. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005;330:843.
17. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITs study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366-72.
18. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Luscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 2003;21:1779-86.

Chapter 4

Self-measurement of blood pressure at home
reduces the number of anti-hypertensive drugs:
results of the HOMERUS-trial

WJ Verberk, AA Kroon, JWM Lenders, AGH Kessels, GA van Montfrans,
AJ Smit, PHM van der Kuy, PJ Nelemans, RJMW Rennenberg, DE Grobbee,
FW Beltman, MA Joore, DEM Brunenberg, C Dirksen, Th Thien, PW de Leeuw
on behalf of the HOMERUS investigators

Abstract

Background

Current evidence is lacking whether self blood pressure measurement (SBPM) is a reliable tool to base antihypertensive treatment on.

Objective

To investigate whether antihypertensive treatment based on SBPM leads to less medication than treatment based on office blood pressure measurement (OBPM) with the same blood pressure (BP) targets and without development of target organ damage (TOD).

Design

Prospective multi-centre randomised clinical trial with a one-year follow-up duration.

Setting

430 mild-to-moderate hypertensive patients were recruited at four university hospitals in the Netherlands and 13 general practitioners practices surrounding these hospitals between April 2002 and October 2003. When eligible for participation, patients were randomised into two treatment groups, either the self pressure group (SP) ($n=216$) or the office pressure (OP) group ($n=214$).

Measurements

Patients from the SP group performed SBPM for seven days (triplicate morning and evening readings) prior to each visit (8 in total). Office blood pressure (three consecutive readings) was obtained for all patients at each visit (10 in total) as well as 24-h ambulatory blood pressure at the start and at the end of the study. Microalbuminuria and echocardiographic left ventricular mass were assessed at the start and at the end of the study for determining the presence of target organ damage.

Intervention

Antihypertensive treatment was initiated according to a standardised schedule based on either SBPM values for the SP group or on OBPM values for the OP group.

Results

Patients from the SP group used less medication than patients from the OP group (treatment intensity: 1.47 vs. 2.48 drug steps; $p<0.001$) and more patients in the SP group could permanently stop their drug treatment (10.7% vs. 1.9%; $p<0.001$). Consequently, this resulted in lower treatment costs for patients in the SP group than for patients in the OP group: \$3464 vs. \$2668 per 100 patients for one month of treatment ($p<0.005$). This did not lead to a significant difference in mean OBPM values or changes in left ventricular mass and microalbuminuria in patients for both groups. However at the end of the trial patients from the SP group showed higher mean 24-h ambulatory blood pressure measurement (ABPM) values than patients from the OP group for systolic (125.9 vs. 123.8 mmHg; $p<0.05$) and diastolic BP (77.2 mmHg vs. 76.1 mmHg; $p<0.05$).

Conclusion

SBPM leads to decreased medication use as compared to OBPM without worse OBPM control or increased TOD but with a slightly elevated ABPM value.

Introduction

As the indications for lowering blood pressure (BP) become increasingly stringent, the associated medication use and costs rise markedly¹. This calls for proper diagnosis and careful selection of patients in whom treatment is really indicated. In this respect, conventional or as called office blood pressure measurements (OBPM) in this paper, potentially have clear disadvantages as they can easily elicit a white coat effect, which may lead to overestimation of a patient's BP² and unnecessary drug prescription. Self blood pressure measurements (SBPM) are less liable to the white coat effect³ and provide a more reliable estimate of a patient's "true" BP. In addition, SBPM correlates better with the development of target organ damage (TOD) than OBPM⁴⁻⁶ and has a high predictive power for the development of cardiovascular events⁷ and cardiovascular mortality^{7,8}. Therefore, SBPM has the potential to identify subjects who do not really need treatment. This may reduce drug use and lead to considerable costs savings without compromising risk.

The Home versus Office MEasurement, Reduction of Unnecessary treatment Study (HOMERUS) was designed to determine whether treatment based on SBPM leads to a decreased drug prescription without an impaired BP control and TOD as compared to treatment based on OBPM.

Methods

The design of the HOMERUS-trial has been described in detail elsewhere⁹. In brief, HOMERUS is a multi-centre, prospective, randomised, double blind trial with a parallel-group design. Patients, aged 18 years and older whose office BP was above 139 mmHg systolic and/or 89 mmHg diastolic were randomly allocated to either the self pressure (SP) group or to the office pressure (OP) group, using a procedure of minimisation¹⁰. If randomised to the SP group, the patient was instructed to start self-measurements of BP at home. In this group, antihypertensive treatment was guided on the results of SBPM. In the OP group, treatment was titrated on the basis of office readings. The treating physician was kept blinded for randomisation and, therefore, unaware whether his patient was treated according to OBPM or SBPM values. In order to maintain masking during follow-up patients were asked not to tell their physician to which group they belonged. In accordance with recommendations at the time of the start of the study, for both groups the target BP was set at 120 to 140 mmHg systolic and 80 to 90 mmHg diastolic and the lower limit at 120 mmHg systolic and 80 mmHg diastolic. At entry into the study, any existing antihypertensive therapy was discontinued whenever possible, and patients entered a placebo run-in period of four weeks duration, before study treatment was initiated. If the treating physician considered interruption of treatment to be

too hazardous the patient was switched immediately to the trial medication. Twenty-four hour ambulatory blood pressure monitoring (ABPM), as a reference standard, and assessment of TOD (heart, kidney) took place at the end of the run-in period and at the end of the trial. Final results of the trial were analysed in two domains: 1) medication use and costs and 2) degree of BP control and TOD.

Blood pressure measurements

At each visit, three consecutive OBPMs were performed in the hospital or at the general practitioners clinic. Patients of the SP group started SBPM three weeks after study entry. SBPM was performed six times a day (three in the morning and three in the evening) for a 7-day period, prior to every visit. Patients were requested to register their self-measurements on a form and to print out each measurement and to deliver the print to the research nurse at the next visit. Both OBPM and SBPM were always performed at the non-dominant arm in sitting position after at least 5 min of rest, using the same fully automated device (Omron HEM-705 CP)¹¹. In addition, ABPM was performed with a Spacelabs automatic device at the start and at the end of the trial. Measurements were taken every 15 min between 07.00 and 23.00h and every 30 min at night. The average daytime ABPM value was calculated from 09.00 to 21.00h on the first day without the initial hour. Average nocturnal ABPM was determined from 0.100 to 0.600h.

Laboratory analyses

Blood was drawn from fasting patients for determination of blood glucose, serum cholesterol (total and HDL-cholesterol) and serum creatinine. Urinary albumin concentration was assessed in one centre from two consecutive 24-h urine collections.

Echocardiography

Left ventricular mass was estimated according to the formula of Devereux¹² and indexed to body surface area. All examinations were recorded on videotape and assessed at the coordinating office by three independent readers. Extra measurements were performed to estimate the intra class correlation as a measure of the magnitude of intra-observer agreement ($r=0.70$; $p<0.01$).

Treatment Protocol

All treatment decisions were taken at the coordinating centre. Antihypertensive treatment was standardised throughout the trial blinded to both the patient and

the treating physician or nurse. Depending on the measured BP level, treatment could be adjusted according to the following schedule:

- Step 1: Lisinopril 10 mg once daily plus one tablet of placebo once daily
- Step 2: Lisinopril 20 mg once daily plus one tablet of placebo once daily
- Step 3: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg
- Step 4: Lisinopril 20 mg once daily plus hydrochlorothiazide 12.5 mg plus amlodipine 5 mg.
- Step 5: Lisinopril 40 mg once daily plus hydrochlorothiazide 12.5 mg plus amlodipine 5 mg
- Step 6: Lisinopril 40 mg once daily plus hydrochlorothiazide 25 mg plus amlodipine 5 mg
- Step 7: Lisinopril 40 mg once daily plus hydrochlorothiazide 25 mg plus amlodipine 10 mg.

When patients were above the target BP (systolic >139 mmHg and/or diastolic >89 mmHg), treatment was intensified by one step, when BP came below the target value (systolic <120 mmHg and diastolic <80 mmHg), treatment was reduced by one step.

In patients in whom an ACE-inhibitor was contra-indicated, lisinopril 10 mg and 20 mg were replaced by atenolol 50 mg and 100 mg, respectively.

The intensity of antihypertensive drug treatment was evaluated as follows: 0.5 was ascribed to a daily dose of 10 mg lisinopril, 50 mg atenolol and 12.5 mg hydrochlorothiazide. A daily dose of 20 mg lisinopril, 100 mg atenolol, 25 mg hydrochlorothiazide and 5mg of amlodipine was calculated as 1. The intensity of combination therapy was calculated with the same weighting of drug doses as above. When patients were untreated this was scored as 0. From all patients medication intake was registered at each visit in order to determine treatment compliance according to pill count.

Additional measurements

Treatment costs

Pharmacy costs were computed for each drug on each visit based on standards of the Dutch healthcare insurance system. Pharmacist's fee amounted to \$7.43 General Practitioner's fee to \$21.38 and physician's fee to \$93.55 in 2004. The costs of one month of treatment with 10 mg/d of lisinopril, 20 mg/d of lisinopril, 12.5 mg/d of hydrochlorothiazide, 25 mg/d of hydrochlorothiazide, 5 mg/d of amlodipine, 10 mg/d of amlodipine, 50 mg/d of atenolol and 100 mg/d of atenolol are \$15, \$18, \$5, \$6, \$15, \$19, \$7 and \$9, respectively.

The costs of the BP monitor was \$59 for one year. This was calculated using the annuity method with a depreciation period of three years, an interest rate of

4.5% and maintenance costs of 8% of the purchase price (\$132). The total costs are reported in US\$ (1 US\$ is 0.76€, January 2004 conversion rate) and medication prices at May 2005 were taken for analysis.

Side-effects of medication

In a subscale of the Bulpitt questionnaire¹³ symptoms of hypertension and side-effects of medication were addressed. This was performed in 356 patients (179 from the SP group) and 177 from the OP group who were included before May 1 2003.

Statistical considerations

Method of randomisation

Patients were randomly allocated to the SP or OP group using the procedure of minimisation¹⁴, taking into account the following pre-specified prognostic factors: hospital or general practitioner, region, gender, age (<40 years, 40-60 years, and >60 years), (a history of) clinical symptoms and whether the patient had a placebo run-in period or not. A blinded person performed the randomisation using dedicated software.

Sample size calculation

To reject the hypothesis of a systolic pressure difference larger than 5 mmHg and/or a diastolic pressure difference larger than 3 mmHg with a significance level of 5% (two-sided) and a power of 80%, 292 randomised patients were needed (standard deviations of systolic and diastolic pressures 15 and 10 mmHg). To allow for a 20% drop-out rate (no endpoints available) 360 patients had to be included.

Data were analysed based on the intention-to-treat principle. In relevant cases a per-protocol analysis was carried out as well. The last observation carried forward (LOCF) method was applied for missing values when data of at least two visits in a row were present. Differences in BP between the two randomised groups were analysed by a multivariate analysis adjusting for baseline BP values, centre, age, gender, run-in period. Other between group comparisons involved the following statistical methods; Student t-test, Mann-Whitney, when not normally distributed, or chi-square for proportions. The longitudinal effects on treatment status were determined with Kaplan-Meier survival estimates and the Log-rank test. A p -value smaller than 0.05 was taken as statistical significance (2-sided).

All statistical calculations were performed using SPSS version 12.0 (SPSS, Inc. Chicago, Illinois).

Results

In total, 459 patients met the inclusion criteria and were considered eligible for the study. Of these 29 did not start trial therapy because they withdrew or refused consent for various reasons. Consequently 430 patients entered the study after a 4 week run-in period and started trial medication (Figure 4.1). The baseline characteristics at inclusion and their distribution over the randomised groups are presented in Table 4.1 showing that groups were comparable.

Figure 4.1 Flow diagram of study subjects.

During the trial 46 patients dropped out (27 in the OP group and 19 in the SP group) since they withdrew consent ($n=44$), had an adverse event ($n=1$) or became pregnant ($n=1$). Reasons for drop-out were that patients felt uncomfortable with the blinded prescribed medication, complained about side-effects, which they attributed to their medication, found the prevalence of visits to the hospital too cumbersome or thought that the additional examinations (echo, ECG and laboratory measurements) were or would be too hazardous. Patients who dropped out from the study did not differ in any characteristics

from patients who fulfilled follow-up, nor were there any between-group differences.

Median follow-up time was 351 days (interquartile range [IQR] 336-366 days) for the OP group and 354 days (IQR, 340-369 days) for the SP group. A number of 20 patients had no run-in period and immediately switched to trial medication ($n=10$ in the SP group and $n=10$ in the OP group).

Table 4.1 Distribution of clinical characteristics at inclusion

Parameter	Total ($n=430$)	OP group ($n=216$)	SP group ($n=214$)
Males [n (%)]	236 (55)	118 (55)	118 (55)
Age [Yr (SD)]	55 (11)	55 (11)	55 (11)
BMI [kg/m ² (SD)]	28 (4)	28 (5)	28 (4)
Smoking [n (%)]	77 (18)	42 (19)	35 (16)
Alcohol [n (%)]	329 (77)	169 (78)	160 (75)
Glucose [mmol/l (SD)]	5.5 (1)	5.4 (1)	5.6 (1)
Cholesterol [mmol/l (SD)]	5.7 (1)	5.7 (1)	5.7 (1)
Creatinine [μ mol/l (SD)]	82 (16)	82 (14)	82 (17)
Microalbuminuria [mg/24h] *	10.3	10.6	10.0
Number of patients on previous antihypertensives [n (%)]			
0 [n (%)]	132 (31)	64 (30)	68 (32)
1 [n (%)]	160 (37)	85 (39)	75 (35)
2 [n (%)]	103 (24)	50 (23)	53 (25)
3 or more [n (%)]	35 (8)	17 (8)	18 (8)
Previous antihypertensive treatment			
Diuretics [n (%)]	116 (27)	55 (25)	61 (29)
ACE-inhibitors [n (%)]	114 (27)	59 (27)	55 (26)
Beta-blockers [n (%)]	120 (28)	57 (26)	63 (29)
Calcium channel blockers [n (%)]	51 (12)	27 (13)	24 (11)
Angiotensin II receptor blockers [n (%)]	65 (15)	35 (16)	30 (14)
Alpha-blockers [n (%)]	8 (2)	6 (3)	2 (1)

BMI indicates body mass index; ACE angiotensin-converting enzyme; * results are given as median.

Treatment Intensity and BP control

Medication use and costs

Figure 4.2 shows that more patients from the SP group than from the OP group could permanently stop their antihypertensive treatment because, without medication, they had BP values within the ranges of 120-140 and 80-90 mmHg for systolic and diastolic pressure respectively (10.7% vs. 1.9%; log-rank $p<0.0003$). In the SP group more patients reached a stabilised treatment level, indicating that treatment steps remained unchanged during the remaining part of the study, than patients from the OP group (54.0% vs. 48.0%; log-rank $p<0.0001$).

Figure 4.2 Kaplan-Meier Estimates of Probability that during follow-up patients could stop antihypertensive drug treatment or reached their final treatment step. P values are of the differences between patients randomised to treatment based on office blood pressure measurement (OP) or on self blood pressure measurement (SP).

Further analysis explored whether region, sex, age, systolic and diastolic BP at the end of the run-in period could predict the permanent discontinuation of antihypertensive drug treatment. In patients from the SP group, the probability of stopping drug treatment increased 1.8-fold (95% confidence interval [CI], 1.3 to 2.4; $p<0.001$) for each 5 mmHg decrement in the systolic SBPM value but did not change with decreasing diastolic SBPM value; the odds ratio was 1.0 (CI 0.6 to 1.6; $p=0.98$). After accounting for the systolic ($p=0.10$) and diastolic office BP ($p=0.58$) value at the end of the run-in period, region ($p=0.58$), sex ($p=0.97$) and age ($p=0.96$), the odds ratio was 1.4 (95% CI, 1.0-2.2; $p=0.08$). This means that, in the SP group, the systolic SBPM value at the end of the run-in period was a reliable predictor for permanent cessation of drug treatment.

In the OP group the odds ratios for stopping treatment, associated with a 5 mmHg lower systolic and diastolic OBPM values at the end of the run-in period were 2.8 (95% CI, 1.2-6.8; $p<0.05$) and 0.9 (95% CI, 0.3-2.8; $p=0.92$) for systolic and diastolic OBPM values, respectively. With adjustment for region ($p=0.77$), sex ($p=0.51$) and age ($p=0.49$) the odds ratios were 3.1 (95% CI, 1.1-8.9; $p<0.05$) and 1.1 (95% CI, 0.3-2.5; $p=0.82$) for systolic and diastolic OBPM values, respectively. Thus in the OP group the systolic OBPM value at the end of the run-in period was a predictor for permanent drug cessation.

Table 4.2 shows that the difference in medication use between the two groups was relatively small at the first month of follow-up but gradually increased to almost one medication intensity step at the final visit. This implies that, on average, the SP group used one drug or one dose less in comparison to the

OP group ($p<0.001$). Significant differences for certain drugs were mainly caused by the fact that patients in the OP group were situated on a higher level of the treatment schedule. At the end of the trial significantly more patients in the OP group than in the SP group received atenolol, which indicates that they had more often contra-indications to lisinopril.

Table 4.2 Antihypertensive drugs for the two treatment groups used during follow-up.

	1 Month	<i>p</i>	2 Month	<i>p</i>	4 month	<i>p</i>	6 Month	<i>p</i>	8 Month	<i>p</i>	10 Month	
	value		value		value		value		value		value	
<i>Treatment score, mean (SD)</i>												
OP group	0.52		0.90		1.78		2.11		2.36		2.48	
	(0.21)		(0.39)		(0.91)		(1.15)		(1.3)		(1.44)	
SP group	0.47	<0.05	0.75	<0.001	1.27	<0.001	1.45	<0.001	1.57	<0.001	1.67	<0.001
	(0.20)		(0.39)		(0.90)		(1.07)		(1.17)		(1.3)	
<i>Study medication % of patients (median dose, mg/d)</i>												
Lisinopril												
OP group	85.3		66.8		61.7		44.2		38.4		34.2	
	(10)		(20)		(20)		(20)		(20)		(20)	
SP group	85.2	0.97	53.3	<0.01	51.5	<0.05	43.1	0.82	41.5	0.54	40.5	0.20
	(10)		(20)		(20)		(20)		(20)		(20)	
Hydrochlorothiazide												
OP group	1.9		7.7		63.3		56.3		46.3		41.6	
	(12.5)		(12.5)		(12.5)		(12.5)		(12.5)		(12.5)	
SP group	0.9	0.40	4.2	0.14	48.5	<0.01	47.0	0.07	42.5	0.45	40.5	0.83
	(12.5)		(12.5)		(12.5)		(12.5)		(12.5)		(12.5)	
Amlodipine												
OP group	0		1.9		41.8		50.5		45.3		37.4	
			(5)		(5)		(5)		(5)		(5)	
SP group	0		0.9	0.40	26.0	<0.01	31.2	<0.001	35.5	0.05	32.0	0.27
			(5)		(5)		(5)		(5)		(5)	
Atenolol												
OP group	4.3		7.7		10.7		15.3		16.3		18.9	
	(50)		(50)		(100)		(100)		(100)		(100)	
SP group	1.4	0.07	4.7	0.21	7.8	<0.32	8.9	0.05	9.0	<0.05	10.0	<0.05
	(50)		(50)		(100)		(100)		(100)		(100)	

OP indicates the office pressure group; SP, self pressure group. Median daily doses of study drugs were compared between both groups, bold printed indicates a significant difference.

Medication costs during the whole study amounted to \$2698 in the OP group and \$2002 in the SP group per 100 patients for one month of treatment, resulting in a significant saving in medication costs of \$696 ($p<0.005$). With inclusion of the fees for pharmacist, costs amounted to \$3553 and \$2700 ($p<0.005$) for the OP and SP group, respectively. The profit in the SP group is partially offset by the cost of the BP device which is \$490 for 100 patients for one month. When corrected for these costs the SP group still has lower treatment costs than the OP group but the difference is not significant (\$3553

vs. \$3190; $p=0.17$). The total number of visits in the trial were similar in the SP and OP group: 2012 vs. 2066 with a mean charge of \$70 and \$71 for the OP and SP group respectively.

Blood pressure control

Figure 4.3 illustrates the time course of BP patterns. Systolic OBPM increased after visit 1 when the run-in period started and regular antihypertensive treatment was discontinued. At visit 3 more patients were hypertensive according to their systolic BP than to their diastolic BP ($n=391$ vs. $n=342$). Both groups showed almost similar BP patterns throughout the trial. Although SBPM followed the same pattern during follow-up as OBPM, at every visit SBPM was significantly lower than OBPM ($p<0.001$). Of the 42 SBPMs that had to be performed prior to each visit, patients measured their BP on average 39.3 times. Table 4.3 illustrates OBPM, SBPM and ABPM values at the end of the run-in period and at the end of the trial. There were no significant differences in OBPM values at the end of the trial but ABPM values were significantly lower for patients in the OP group than for patients in the SP group.

In the OP group 409 times (24%) treatment decisions were based on elevated systolic BP, 48 times (3%) on elevated diastolic BP only and 699 times (41%) on both elevated systolic and diastolic BP values. In the SP group 357 times (21%) treatment decisions were based on systolic BP, 34 times (2%) because of only elevated diastolic BP and 398 times (23%) because both systolic BP and diastolic BP values were increased.

After one year of follow-up, 33 patients (8%) had refractory hypertension as defined by an OBPM value greater than 160 mmHg systolic and/or 100 mmHg diastolic while patients were on step 4 or beyond of the treatment schedule. Of these refractory hypertensive patients, 17 (8%) belonged to the OP group and 16 (7%) to the SP group ($p=0.86$). At the end of the trial 106 patients (50%) in the OP group had an OBPM value lower than 140/90 mmHg while in the SP group 160 patients (74%) reached their SBPM target on which their treatment was based, this were significantly more patients than in the OP group ($p<0.001$).

Figure 4.3 Average office, self and 24-h ambulatory blood pressure (ABPM) patterns of 1 year follow-up for the OP group (○) and SP group (●). Values are given as mean and S.E.M.

Target organ damage

Changes in left ventricular mass index (LVMI) were similar in both groups: $-6.5 \text{ g/m}^2 \pm 1.7$ (from 98.3 g/m^2 to 91.8 g/m^2) vs. $-5.6 \pm 1.7 \text{ g/m}^2$ (from 96.4 g/m^2 to 90.8 g/m^2) for the OP and SP group, respectively ($p=0.72$). Likewise, median changes in urinary microalbumin concentration were similar: from 10.0 mg/24h to 8.3 mg/24h and from 10.7 mg/24h to 9.2 mg/24h for the OP and SP group, respectively ($p=0.87$). Within group reductions in LVMI and microalbuminuria concentrations were significant for both randomised groups ($p<0.001$). No

significant differences between groups were found for other laboratory variables.

Table 4.3 Blood pressure and heart rate values (mean $\pm$ SD) at the end of the run-in period and at the end of the trial.

BP, mmHg	OP group (<i>n</i> =214)	SP group (<i>n</i> =216)	Difference mean [OP-SP] (95% CI)	<i>p</i> value
OBPM Systolic				
End run-in	165.1 $\pm$ 20.8	166.2 $\pm$ 19.3	-1.0 (-4.8 to 2.8)	0.43
End trial	142.2 $\pm$ 20.0	143.8 $\pm$ 18.4	-1.6 (-5.3 to 2.0)	0.28
Diastolic				
End run-in	97.8 $\pm$ 10.8	97.1 $\pm$ 9.9	0.7 (-1.2 to 2.7)	0.54
End trial	84.3 $\pm$ 9.6	85.4 $\pm$ 10.4	-1.0 (-2.9 to 0.9)	0.13
SBPM Systolic				
End run-in		156.1 $\pm$ 16.9		
End trial		134.3 $\pm$ 12.2		
Diastolic				
End run-in		92.8 $\pm$ 9.0		
End trial		80.9 $\pm$ 8.1		
ABPM 24-hour Systolic				
End run-in	143.4 $\pm$ 13.5	143.7 $\pm$ 13.8	0.4 (-3.0 to 2.3)	0.78
End trial	123.8 $\pm$ 12.2	125.9 $\pm$ 9.0	-2.1 (-4.3 to 0.0)	0.03
Diastolic				
End run-in	88.4 $\pm$ 8.8	88.1 $\pm$ 9.7	0.3 (-1.5 to 2.1)	0.92
End trial	76.1 $\pm$ 7.9	77.2 $\pm$ 7.4	-1.1 (-2.7 to 0.4)	0.04
ABPM day Systolic				
End run-in	149.5 $\pm$ 14.5	149.3 $\pm$ 14.8	0.1 (-2.8 to 3.0)	0.96
End trial	129.1 $\pm$ 12.8	131.2 $\pm$ 10.7	-2.2 (-4.5 to 0.2)	0.03
Diastolic				
End run-in	93.6 $\pm$ 9.3	92.7 $\pm$ 10.5	1.0 (-1.0 to 2.9)	0.48
End trial	80.4 $\pm$ 8.4	81.6 $\pm$ 8.6	-1.2 (-2.9 to 0.5)	0.03
ABPM night Systolic				
End run-in	127.6 $\pm$ 15.8	127.9 $\pm$ 14.5	-0.3 (-3.3 to 2.7)	0.95
End trial	110.1 $\pm$ 12.5	112.3 $\pm$ 10.1	-2.2 (-4.5 to 0.1)	0.02
Diastolic				
End run-in	76.1 $\pm$ 10.4	76.2 $\pm$ 10.5	-0.1 (-2.2 to 2.0)	0.89
End trial	65.5 $\pm$ 8.8	66.4 $\pm$ 7.5	-1.0 (-2.6 to 0.7)	0.12

OBPM indicates office blood pressure measurement; SBPM, self blood pressure measurement; ABPM, ambulatory blood pressure measurement CI, confidence interval. BP values are adjusted for baseline value, sex, age, body mass index, region of inclusion and for a run-in period (yes or no). Bold printed indicates a significant between-group difference ($p < 0.05$). All with-in group changes were significant ($p < 0.001$)

Pill-count

Pill counts, which were assessed in all patients, indicated that medication intake was similar in both arms: 88.1% in the OP group vs. 87.3 in the SP group ($p=0.62$).

Side-effects

The reported frequency of symptoms and side-effects per visit is presented in Table 4.4. Headaches, joint complaints, flushing of face or neck, light-headedness and sleepiness were the most frequently mentioned symptoms (>35%). As the study progressed, a small tendency to report less symptoms was observed. This applied to both groups.

Table 4.4 Frequency of symptoms and side-effects (%) per visit per group

Symptoms and side-effects	1 month		3 months		7 months		12 months	
	SP	OP	SP	OP	SP	OP	SP	OP
Light-headedness	43	37	36	39	39	35	40	32
Sleepy during the day	42	44	41	42	38	40	42	40
Weakness in the limbs	22	22	23	22	25	26	22	23
Blurring of vision	38	32	30	30	29	30	30	24
Short of breath	8	13	8	14	9	9	13	12
Swollen ankles	19	13	17	14	15	14	12	15
Loose or liquid motions	18	21	21	25	19	16	19	22
Constipation	6	5	7	4	11	4	14	8
Dry mouth	34	29	27	24	25	21	25	14
Bad taste	15	10	8	11	11	10	9	5
Blocked or runny nose	37	36	36	39	32	33	36	30
Dry cough	26	29	38	43	39	43	41	37
Flushing face or neck	44	39	40	38	30	39	32	30
Nightmares	11	7	10	11	7	6	10	9
Sick or vomited	10	8	9	10	11	8	7	6
Rash	13	22	19	13	16	12	13	10
Itching	22	24	24	19	20	11	27	20
White fingers	17	20	14	18	21	21	20	25
Headaches	55	58	45	39	38	31	34	23
Dry painful eyes	23	19	21	18	21	21	23	16
Palpitations	33	29	20	26	20	18	16	18
Medication not taken*	3	6	2	3	7	6	5	2
Muscle spasm	24	27	21	26	30	25	30	26
Joint complaints	43	35	38	35	37	29	41	35
Shortness of breath	20	22	18	19	18	20	20	16
Went to doctor for complaints	41	38	25	26	34	24	26	22

SP indicates self pressure group; OP, office pressure group; * Because of side-effects

Discussion

Our results show that adjustment of antihypertensive therapy based on SBPM can reduce the number of drugs without loss of OBPM control or an increase in the number of refractory hypertensive patients but with slightly increased ABPM values as compared to patients who were treated based on OBPM values. Moreover, there was no increase in target organ damage. Patients of the SP group were more likely to reach the target BP value and reached earlier and more frequently a point when treatment was stabilised than patients in the OP group. In addition, significantly more patients in the SP group could stop their antihypertensive treatment permanently indicating that SBPM is a valuable tool to prevent unnecessary drug prescription, mainly caused by the white coat effect.

This study must be interpreted within the context of its limitations. BP measurements were not performed with a memory-equipped device, which may leave room for observer bias; patients may have measured BP several times more and have selected three preferred measurements. In some general practices OBPM was performed by a nurse instead of a physician, which, may have resulted in lower BP values¹⁵. Patients were equally divided between the two groups in these practices but as overall differences between OBPM and SBPM values decreased, some dilution cannot be excluded. Furthermore, there may have been differences in the way patients experienced OBPM. Patients from the OP group knew that their treatment was based on these measurements while patients from the SP group knew that their OBPM values had no consequences for treatment.

The present study chose to take 140/90 mmHg as a threshold for SBPM instead of the 135/85 mmHg as is nowadays recommended¹⁶, this may have led to underestimation of SBPM values as compared to OBPM. However, there were several reasons for taking 140/90 mmHg as threshold values for SBPM: first, at the time the protocol for HOMERUS was written there was no agreement on what should be the upper limit for SBPM¹⁷ as only some cross-sectional studies¹⁸⁻²³ and one longitudinal study²⁴ addressing this subject had been performed. Second, the guidelines that recommend 135/85 mmHg as the threshold value for SBPM prescribes that OBPM is performed with a mercury sphygmomanometer and the SBPM with an oscillometric automatic device. However, in the present study both SBPM and OBPM are performed with the oscillometric automatic device so that there were no differences in BP values caused by the device. Third, the recommendations for OBPM prescribe that two measurements should be performed²⁵. In the present study, three measurements were performed, which regularly leads to lower average OBPM values as the first measurement normally is higher than subsequent ones²⁶. Lower OBPM values will dilute the differences between OBPM and SBPM.

Recently, the results of the THOP-trial²⁷ were published which showed that patients whose medical treatment was based on SBPM had poorer OBPM and ABPM values than patients who had their treatment based on OBPM. Although the THOP-trial seems largely similar to HOMERUS, there were some differences that may have been essential for the outcome and, therefore, explain some different results. Firstly, in the THOP-trial treatment was based on diastolic BP (<90 mmHg) only, as at that time the World Health Organization exclusively defined hypertension on the basis of diastolic BP^{28,29}. The HOMERUS-trial, however, considered both systolic and diastolic BP. Baseline characteristics showed that more patients were hypertensive according to their systolic BP than to their diastolic BP. In addition, during follow up a quarter of all treatment decisions were based on elevated systolic BP only. Although the number of systolic based treatment decisions did not differ between the groups, this more intensified treatment caused a further decrease in overall BP value and, therefore, may also have decreased differences between both groups. Moreover, for optimal management of hypertension well-controlled systolic BP is important as it has a significantly stronger relationship to the risk of cardiovascular or all-cause death³⁰ than diastolic BP. Secondly, in the THOP trial OBPM was performed with a manual mercury sphygmomanometer instead of the automatic BP device that was used by the patients for SBPM. Use of different devices complicates comparison between both strategies and, in addition, manual sphygmomanometers are more liable to observer bias³¹.

The cost-effectiveness of SBPM has also been evaluated in the THOP trial. Our study confirmed the finding of a significant reduction in medication intensity and a reduction in medication costs. The maximum difference in treatment costs was obtained at the end of the study. When these costs were extrapolated to the next year this would lead to an increased cost reduction for treatment in favour of the SP group. When extrapolated to the society at large and to chronic treatment, this would imply a major reduction in healthcare costs. The calculated cost saving is certainly not a robust point estimate since both drug costs and electronic BP devices are rapidly reducing in a fluctuating market. Moreover, in view of potential adverse effects and patient burden, any reduction in medication need is beneficial.

ABPM values differed between the SP and OP group and as ABPM is still considered to be the gold standard for blood pressure measurement this suggests that antihypertensive treatment based on SBPM leads to worse controlled BP as compared to OBPM based treatment. However, during the trial ABPM was performed only twice and reproducibility of ABPM is poor. Intra-individual differences between one ABPM and another can also result from factors such as differences in daily activities between both recording days, lower accuracy of the ABPM device at higher BP and differences in quality of sleep³². Obviously, the differences in mean ABPM-values between both

groups, although they are small and therefore may not seem relevant for a patient as individual, cannot be ignored as these differences can have serious consequences with respect to cardiovascular events in future for the population at large. A meta-analysis of individual data for one million adults in 61 prospective studies showed that even a 2 mmHg lower systolic BP value would eventually lead to a 10% lower stroke mortality and about 7% lower mortality from ischemic heart diseases or other vascular causes in middle age patients³³. In conclusion, the findings in this large randomised trial show that in a population of mild-to-moderate hypertensive subjects without significant co-morbidity, antihypertensive treatment based on SBPM is not associated with worse OBPM control nor with TOD, or with an increased number of refractory hypertensive patients as compared to treatment based on OBPM. In addition, SBPM does lead to decreased use of medication and prevents unnecessary drug use and, therefore, leads to less overall healthcare costs.

The advantages for SBPM, together with our findings, support the use of SBPM for implementation into regular clinical care to improve overall BP control and to prevent unnecessary treatment subscriptions, with its associated healthcare costs. However, the fact that the ambulatory BP was less well controlled in patients from the SP group than in the OP group indicates that ABPM values of both groups probably would be more similar when SBPM values of 135 mmHg systolic and 85 mmHg diastolic were used as the threshold values for normal BP.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
2. Pickering TG, Gerin W, Schwartz AR. What is the white-coat effect and how should it be measured? *Blood Press Monit* 2002;7:293-300.
3. Stergiou GS, Efstathiou SP, Argyraki CK, Roussias LG, Mountokalakis TD. White coat effect in treated versus untreated hypertensive individuals: a case-control study using ambulatory and home blood pressure monitoring. *Am J Hypertens* 2004;17:124-8.
4. Staessen JA, Byttebier G, Buntinx F, Celis H, O'Brien ET, Fagard R. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement. A randomized controlled trial. *Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators. JAMA* 1997;278:1065-72.
5. Mule G, Caimi G, Cottone S, Nardi E, Andronico G, Piazza G, Volpe V, Federico MR, Cerasola G. Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk* 2002;9:123-9.
6. Kario K, Shimada K, Pickering TG. Clinical implication of morning blood pressure surge in hypertension. *J Cardiovasc Pharmacol* 2003;42 Suppl 1:S87-91.
7. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998;16:971-5.
8. Cuspidi C, Michev I, Meani S, Salerno M, Valerio C, Fusi V, Bertazzoli G, Magrini F, Zanchetti A. Left ventricular hypertrophy in treated hypertensive patients with good blood pressure control outside the clinic, but poor clinic blood pressure control. *J Hypertens* 2003;21:1575-81.
9. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
10. Verberk WJ, Kroon AA, Kessels AG, Nelemans PJ, Van Ree JW, Lenders JW, Thien T, Bakx JC, Van Montfrans GA, Smit AJ, Beltman FW, De Leeuw PW. Comparison of randomization techniques for clinical trials with data from the HOMERUS-trial. *Blood Press* 2005;14:306-14.
11. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *PG - Blood Press Monit* 1996 Feb;1:55-61. 1996:55-61.
12. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613-8.
13. Bulpitt CJ, Fletcher AE. The measurement of quality of life in hypertensive patients: a practical approach. *Br J Clin Pharmacol* 1990;30:353-64.
14. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-15.
15. La Batide-Alanore A, Chatellier G, Bobrie G, Fofol I, Plouin PF. Comparison of nurse- and physician-determined clinic blood pressure levels in patients referred to a hypertension clinic: implications for subsequent management. *J Hypertens* 2000;18:391-8.
16. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;23:697-701.
17. Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *Am J Hypertens* 1996;9:1-11.

18. de Gaudemaris R, Chau NP, Mallion JM. Home blood pressure: variability, comparison with office readings and proposal for reference values. Groupe de la Mesure, French Society of Hypertension. *J Hypertens* 1994;12:831-8.
19. Imai Y, Satoh H, Nagai K, Sakuma M, Sakuma H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N, Yabe T, Nishiyama A, Nakatsuka H, Koyama T, Abe K. Characteristics of a community-based distribution of home blood pressure in Ohasama in northern Japan. *J Hypertens* 1993;11:1441-9.
20. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens* 1995;13:1377-90.
21. Mejia AD, Julius S, Jones KA, Schork NJ, Kneisley J. The Tecumseh Blood Pressure Study. Normative data on blood pressure self-determination. *Arch Intern Med* 1990;150:1209-13.
22. Weisser B, Grune S, Burger R, Blickenstorfer H, Iseli J, Michelsen SH, Opravil R, Rageth S, Sturzenegger ER, Walker P, Widmer W, Vetter W. The Dubendorf Study: a population-based investigation on normal values of blood pressure self-measurement. *J Hum Hypertens* 1994;8:227-31.
23. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian Population Study. *Blood Press Monit* 1996;1:13-26.
24. Tsuji I, Imai Y, Nagai K, Ohkubo T, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Proposal of reference values for home blood pressure measurement: prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am J Hypertens* 1997;10:409-18.
25. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48.
26. Stergiou GS, Thomopoulou GC, Skeva, II, Mountokalakis TD. Home blood pressure normalcy: the Didima study. *Am J Hypertens* 2000;13:678-85.
27. Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G, O'Brien ET. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA* 2004;291:955-64.
28. Hypertension control. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1996;862:1-83.
29. 1993 guidelines for the management of mild hypertension. Memorandum from a World Health Organization/International Society of Hypertension meeting. Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. *Hypertension* 1993;22:392-403.
30. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777-83.
31. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
32. van der Steen MS, Lenders JW, Graafsmas SJ, den Arend J, Thien T. Reproducibility of ambulatory blood pressure monitoring in daily practice. *J Hum Hypertens* 1999;13:303-8.
33. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.

Chapter 5

The optimal scheme of self blood pressure measurement as determined from ambulatory blood pressure recordings

WJ Verberk, AA Kroon, AGH Kessels, JWM Lenders, Th Thien,
GA van Montfrans, AJ Smit, PW de Leeuw

J of Hypertension: accepted for publication

Abstract

Objective

To determine how many self-measurements of blood pressure (BP) should be taken at home in order to obtain a reliable estimate of a patient's BP.

Design

Participants performed self blood pressure measurement (SBPM) for seven days (triplicate morning and evening readings). In all of them, office blood pressure (three consecutive readings) and 24-h ambulatory blood pressure was measured as well. Average SBPM values, obtained from several combinations of readings, were correlated with the results of ambulatory blood pressure measurement (ABPM). In addition, we assessed whether certain patient characteristics would influence such correlations.

Settings

Patients were recruited at hospital or general practice.

Patients

A total of 216 untreated hypertensive patients.

Results

The average SBPM value calculated from day 3 to day 7, omitting the first measurement of each morning and evening session, gave the best correlation with 24-h ABPM ($r=0.70$). However, similar results were obtained from a SBPM value averaged from day 3 until 5 without the first measurement of each triplicate session. Overall, younger patients had significantly better correlations than older ones. Women had significantly better correlations with ABPM than men for systolic morning and daytime SBPM, whereas men had significantly better correlations for daytime and evening diastolic SBPM ($p<0.001$). In addition, all correlations increased with lower systolic OBPM values.

Conclusions

A minimum number of five days of measurement is recommended to obtain a reliable estimate of a patient's usual BP. On each day, three consecutive morning and evening measurements should be performed. For calculating the average SBPM, the first two days and the first measurement of each triplicate measurements should be discarded. Moreover, patient characteristics may have an impact on the number of necessary self-measurements. However, because adhering to these recommendations will make SBPM a time-consuming procedure, this type of measurement should be performed only when a decision about starting or changing antihypertensive therapy is needed or in the case of special patient groups.

Introduction

Self blood pressure measurement (SBPM) is becoming increasingly popular. Indeed, SBPM has many advantages above office blood pressure measurement (OBPM) such as the elimination of the white coat effect¹ and a better correlation with both ambulatory blood pressure measurements² and target organ damage³⁻⁶. These considerations have led several authoritative bodies to recommend the use of SBPM for clinical practice^{7,8}.

Despite the popularity of SBPM, there are no evidence-based guidelines with respect to the number of SBPMs that should be obtained for optimal assessment of a patient's usual blood pressure (BP). Although several studies have addressed this issue⁹⁻¹³, their protocols varied widely in terms of number of subjects, sort of analysis and methods of BP measurement. Not surprisingly, therefore, these investigations resulted in different outcomes. Recommendations diverged from taking the average of two readings for three consecutive measurement days¹⁰ to more than 14 days of SBPM¹². This makes it difficult to reach consensus and give recommendations that are based on clinical evidence. Moreover, in these studies patient characteristics (gender, age etc.) have not sufficiently been taken into account.

In the present study, we have tried to establish the optimal number of SBPM by comparing SBPM results directly to data obtained with 24-h ambulatory blood pressure measurement (ABPM), which is still considered to be the 'gold standard' in BP measurement. In most studies ABPM appeared to correlate better with target organ damage^{14,15} and to be superior when it comes to prediction of cardiovascular risk than conventional BP measurements^{14,16-18}. In contrast to earlier studies, we have also investigated the influence of certain patient characteristics on the correlation between SBPM and ABPM.

Patients and methods

Patients

Patients who participated in this study formed a sub-population of the HOMERUS-trial, the design of which has been described previously¹⁹. Altogether, 216 mild to moderate hypertensive patients (118 male, 55%) with a mean age of 55 ± 11 years and a body mass index of 28 ± 4 kg/m², who all performed SBPM, were available for analysis. Patients had a mean OBPM of 166 ± 19 / 97 ± 10 mmHg without antihypertensive treatment. As part of the HOMERUS-protocol, echocardiography and assessment of urinary micro-albumin excretion were performed to estimate the degree of target organ damage. All patients gave their informed consent and the medical ethics committee approved the study protocol.

Blood pressure measurements

Triplicate OBPMs were taken at the hospital or in the general practitioners office when they were without antihypertensive therapy for a period of at least four weeks. SBPM was performed, at the patient's home, six times a day (three measurements in the morning and three in the evening) for a 7-day period prior to the patient's visit to the office. Morning measurements were performed after voiding and before breakfast. Each individual was requested to register his/her self-measurements on a form and, additionally, to print out all measurements. Both OBPM and SBPM were performed at the patient's non-dominant arm, in sitting position, after 5 min of rest with 1 min between the measurements and using the same fully automated device (Omron HEM-705 CP). This device has passed the validation protocol of the British Hypertension Society²⁰. Additionally, ABPM was performed with a Spacelabs automatic device. BP was measured every 15 min between 07.00 and 23.00h and every 30 min during night time. The average daytime ABPM value was calculated from 09.00 to 21.00 h on the first day and the average nocturnal ABPM was determined from 0.100 to 0.600 h according to ESH recommendations²¹. In all registrations, the initial hour after the device had been hooked up was omitted from analysis.

Statistical analysis

The relationship between SBPM and ABPM was analysed for several combinations of ABPM and SBPM data. Average ABPM and SBPM values obtained from morning, evening and daytime (average of morning and evening data) measurements were compared. Regression analysis was applied to assess the relationship between self-measured blood pressure and ABPM. Results were expressed as the correlation coefficient r . Groups were compared according to the following characteristics: age (three different age groups; <50, 50-60, >60 years), gender, level of systolic and diastolic mean OBPM (in quartiles) and for a combination of age (<50 and $\geq$ 50 years) and gender. For all tests, we examined whether the highest correlation was significantly different from the other ones. This was performed by bootstrap simulation²². Statistical calculations were performed using SPSS version 12.0 (SPSS, Inc. Chicago, Illinois).

Results

Figure 5.1 shows that on all seven days of SBPM, the first measurement of each triplicate is significantly higher than subsequent ones for both morning and evening systolic pressure ($p < 0.001$) and for most diastolic BP measurements. BP measurements on the first day were significantly higher

than measurements on subsequent days ($p<0.05$). Overall, evening self-measurements were significantly higher than morning measurements for systolic ($p<0.001$) but not for diastolic BP.

Figure 5.1 Triplicate morning and evening self blood pressure measurements assessed during a 7-day period among patients without antihypertensive treatment. Results are shown as mean $\pm$ SEM. * indicates that measurements are significantly higher than subsequent ones ($p<0.001$).

Correlations of SBPM with ABPM

Initial analyses were performed with either 24-h ABPM or daytime ABPM or nocturnal ABPM as the independent variable. The correlations of SBPM data with those from 24-h, daytime and nocturnal ABPM are illustrated in Table 5.1. Results indicate that there were no significant differences between morning, day and nocturnal correlations and that SBPM tends to correlate better, although not significantly so, with 24-h ABPM ($r=0.70$, for the highest systolic correlation) than with daytime ABPM ($r=0.65$) or nocturnal ABPM ($r=0.60$). Consequently, we further used 24-h ABPM only as the comparator. Taking all measurements into consideration, the best correlations are obtained when SBPM is determined during seven days of measurement, omitting the first two days. Bootstrap analysis showed that significant differences from the highest correlation started to occur when less than five days of SBPM are available.

Overall, correlations tend to improve for all values when the results of the first two days of measurement are omitted (with the r -value rising by 0.01 to 0.03) and/or when the first measurement of each triplicate session is discarded (r -value improving by 0.01 to 0.04) but none of these changes was statistically significant.

Effect of patient characteristics

Gender

Figure 5.2 illustrates that women who are performing SBPM have a significantly better correlation to 24-h ABPM of both daytime and morning systolic SBPM ($p < 0.05$) than men, whereas men have a better correlation for daytime and evening diastolic BP ($p < 0.001$). Although in men the evening correlation is significantly better than the morning correlation for systolic BP ($p < 0.05$), both morning and evening correlations were significantly lower than daytime correlations ($p < 0.05$). Women, on the other hand, have significantly better morning than evening correlations for both systolic ($p < 0.001$) and diastolic BP ($p < 0.05$) and this morning correlation did not differ from the daytime SBPM correlation. Bootstrap analysis revealed that in men no significant intra-group differences from the highest correlation occurred until the measurement period lasted only two days whereas women have to measure for at least four days.

Age

After dividing the study population into three groups according to age (Figure 5.3), the highest correlations were obtained in patients younger than 50 years of age. In particular, correlations for systolic SBPM were significantly higher in this group than in patients who were 50 to 60 years old ($p < 0.05$). However, they were not when compared to patients above 60 years. Diastolic SBPM correlated significantly higher with ABPM in patients under 50 years as compared to both older age groups ($p < 0.001$). Intra-group analysis showed that in all three age groups the highest correlation value did not differ significantly from other correlations.

Table 5.1 Correlation coefficients (r) of self blood pressure measurement (SBPM) values with 24-h, daytime or nocturnal ambulatory blood pressure measurements (ABPM).

	24-h ABPM						Daytime ABPM						Nocturnal ABPM					
	Day			Evening			Day			Morning			Day			Morning		
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Day 1-7	0.70	0.69	0.69	0.64	0.62	0.63	0.65	0.66	0.63	0.63	0.65	0.60	0.59	0.57	0.59	0.56	0.52	0.52
Day 2-7	0.70	0.69	0.68	0.65	0.62	0.65	0.63	0.66	0.63	0.64	0.64	0.61	0.60	0.59	0.58	0.55	0.51	0.51
Day 3-7	0.71	0.69	0.69	0.68	0.64	0.62	0.66	0.67	0.65	0.65	0.65	0.59	0.60	0.59	0.58	0.55	0.52	0.52
Day 4-7	0.71	0.70	0.69	0.68	0.62	0.60	0.66	0.67	0.65	0.64	0.64	0.60	0.61	0.59	0.59	0.54	0.50	0.50
Day 5-7	0.69	0.68	0.68	0.66	0.57	0.62	0.62	0.66	0.62	0.62	0.56	0.56	0.60	0.58	0.59	0.53	0.48	0.48
Day 1-6	0.69	0.69	0.67	0.68	0.64	0.62	0.64	0.66	0.62	0.64	0.58	0.61	0.60	0.58	0.56	0.53	0.52	0.52
Day 2-6	0.69	0.69	0.67	0.67	0.65	0.62	0.65	0.66	0.62	0.63	0.60	0.62	0.59	0.58	0.56	0.55	0.51	0.51
Day 3-6	0.71	0.69	0.68	0.67	0.64	0.63	0.66	0.67	0.63	0.64	0.59	0.62	0.60	0.58	0.57	0.55	0.52	0.52
Day 4-6	0.70	0.69	0.68	0.67	0.62	0.61	0.66	0.67	0.64	0.63	0.58	0.61	0.60	0.58	0.57	0.54	0.50	0.50
Day 1-5	0.69	0.69	0.67	0.67	0.64	0.62	0.63	0.66	0.62	0.63	0.58	0.61	0.59	0.58	0.56	0.55	0.52	0.52
Day 2-5	0.69	0.69	0.66	0.66	0.65	0.62	0.64	0.66	0.61	0.62	0.60	0.62	0.59	0.58	0.56	0.54	0.52	0.52
Day 3-5	0.71	0.69	0.68	0.66	0.65	0.64	0.66	0.66	0.63	0.63	0.60	0.63	0.59	0.58	0.57	0.55	0.53	0.53
Day 1-4	0.68	0.66	0.66	0.62	0.60	0.62	0.63	0.63	0.61	0.62	0.57	0.58	0.58	0.56	0.55	0.54	0.50	0.50
Day 2-4	0.69	0.66	0.66	0.65	0.63	0.60	0.62	0.62	0.61	0.61	0.59	0.58	0.57	0.55	0.55	0.53	0.50	0.50
Day 1-3	0.66	0.66	0.63	0.66	0.61	0.58	0.60	0.63	0.57	0.62	0.56	0.57	0.55	0.56	0.53	0.52	0.48	0.48
Day 2-3	0.66	0.64	0.62	0.62	0.61	0.57	0.60	0.61	0.56	0.58	0.57	0.55	0.55	0.54	0.54	0.49	0.46	0.46
Day 3	0.66	0.62	0.62	0.59	0.56	0.61	0.60	0.60	0.57	0.57	0.55	0.54	0.54	0.51	0.51	0.48	0.49	0.45
Day 1-2	0.62	0.63	0.60	0.62	0.57	0.54	0.57	0.61	0.54	0.58	0.52	0.53	0.53	0.53	0.51	0.54	0.50	0.45
Day 2	0.61	0.57	0.56	0.54	0.57	0.49	0.55	0.55	0.49	0.49	0.53	0.49	0.52	0.50	0.51	0.49	0.47	0.42
Day 1	0.57	0.61	0.57	0.65	0.48	0.53	0.53	0.59	0.53	0.62	0.47	0.47	0.47	0.49	0.47	0.56	0.48	0.38

Average self blood pressure measurement (SBPM) values were determined from triplicate morning and/or evening measurements. The first measurement from each triplicate session was discarded. Day 1-7 indicates the average SBPM value calculated from day 1 until day 7; Day 2-7, the average SBPM value calculated from the second until the 7th day and so on. Numbers in bold indicate that compared to day 3-7 a significant difference ($p < 0.05$) was found with the bootstrap analysis.

Office blood pressure

Figure 5.4 illustrates the study population broken down into four groups according to their average systolic OBPM. Systolic BP correlations of the two groups with the lowest systolic OBPM values (122-153 and 154-165 mmHg) were significantly higher than the correlations of the two groups with the highest ones (166-179 mmHg, $p<0.05$ and 180-221 mmHg, $p<0.001$). These differences were not apparent with respect to diastolic BP.

Figure 5.2 Correlation coefficients (*r-value*) of daytime, morning and evening self blood pressure measurements (SBPM) to 24-h ambulatory blood pressure measurements (ABPM) in women (■; $n=113$) and men (□; $n=94$) patients for both systolic and diastolic blood pressure.

Figure 5.3 Correlation coefficient (r -value) of daytime self blood pressure measurements (SBPM) to 24-h ambulatory blood pressure measurements (ABPM) for three different age groups, patients <50 years ($\square$; $n=57$), between and including 50 and 60 years ($\blacksquare$; $n=113$) and patients older than 60 years ($\circ$; $n=74$), for systolic and diastolic blood pressure.

Correlations of SBPM with target organ damage

Correlations of SBPM with LVMI were low (r ranged 0.10 to 0.25) for both systolic and diastolic SBPM values and did not differ among days of measurement. The same held true for urinary micro-albumin concentration. Neither 24-h ABPM or OBPM showed any significant relationship with left ventricular mass index or with urinary micro-albumin excretion.

Figure 5.4 Correlation coefficient (r -value) of daytime self blood pressure measurements (SBPM) to 24-h ambulatory blood pressure measurements (ABPM) for four different groups, separated according to their average systolic blood pressure value as measured in the physician's office. The systolic blood pressure values ranged from 122-153 mmHg ($\square$; $n=52$), 154-165 mmHg ($\blacksquare$; $n=52$), 166-179 mmHg ($\circ$; $n=52$) and 180-221 mmHg ($\bullet$; $n=51$).

Discussion

The present study shows that the best correlation of SBPM with 24-h ABPM was obtained when SBPM was performed during a 7-day period and the data of the first two days and the first measurement of each triplicate session were discarded. However, similar results were obtained from a minimum number of five days of measurement without the results of the first two days and the first measurement of each triplicate session. Correlations consequently improved, though not always significantly, when the first two days of measurement, and/or the first measurement of each triplicate session were discarded. The highest correlations were obtained when SBPM was compared with 24-h ABPM, but these correlations did not significantly deviate from correlations of SBPM with either daytime or nocturnal ABPM values. When analysed according to gender, data suggest that in men it is not sufficient to perform morning measurements only as both morning and evening correlations differ significantly from daytime correlations. Moreover, patients with lower systolic OBPM had significantly higher correlations than those with higher systolic OBPM and younger patients (< 50 years) had correlations which were significantly higher than those in the elderly. This suggests that patient characteristics should be taken into account when it comes to recommendations about SBPM. Apparently, variables such as age, gender and systolic OBPM have a major impact on the correlation between SBPM and ABPM. There was a low correlation of SBPM with target organ damage that did not change with days and number of measurements.

Our study should be interpreted in the context of its limitations. Discarding the first two days of measurement and the first measurement of each triplicate session improved the correlations but not significantly so. This may, therefore, indicate that it is not absolutely necessary to recommend to omit these measurements. However, we cannot exclude that in a larger group of subjects differences would become statistically significant. Moreover, by omitting these first readings one obtains a more stable estimate of a patient's BP.

Another limitation is that one should preferably base the number of necessary SBPMs on prognostic studies in which the number of SBPMs can be related to cardiovascular events. Such a study has been performed by Ohkubo *et al.*¹². In that study, SBPM consisted of approximately 14 measurements during a period of two weeks. The data were related to the incidence of stroke during 10.6 years of follow-up. However, over such a long period of time, substantial changes in BP may have occurred. In addition, the population had a high mean age (61 y) and largely contained women (67%). Therefore, these results should be interpreted with caution. Alternatively, one may suggest that recommendations concerning SBPM should be based on its relationship with organ damage. However, a correlation with BP and organ damage may not be readily apparent as organ damage develops over a long period of time and it

depends on when BP is taken whether a correlation will be found or not. In the present study, we failed to find correlations with either left ventricular mass index or micro-albuminuria. However, at the time the degree of organ damage was determined, patients had just finished a placebo run-in period of four weeks during which previous antihypertensive treatment had been stopped. It is not surprising, therefore, that we could not find a relationship of SBPM data with target organ damage since the latter better reflected BP status before enrolment into the study. Thus, due to the specific design of this study we were unable to correlate SBPM data with the degree of target organ damage. This paper should, therefore, be considered merely as a contribution as to how the most reliable BP value at home should be obtained.

In recent years, several studies have addressed the optimal number of measurements in SBPM but these differed from our study in some essential aspects. A few based their recommendations on single readings^{10,12} even though it is generally accepted to take at least two consecutive measurements²¹. Celis and co-workers compared their SBPM results to OBPM data while ABPM is a more reliable method of BP measurement⁹. Indeed, an important reason to implement SBPM in healthcare is that it is supposed to better reflect a patient's usual BP than OBPM and thus comparing SBPM to OBPM in order to give recommendations is not appropriate. The study of Stergiou *et al.*¹³ resembles ours most but it differs in various aspects as well. Like us, these investigators correlated SBPM to ABPM and found that measurements on the first day were higher than those on subsequent days and, therefore, they recommended omitting these measurements. Different from our study, however, is that they instructed their patients to perform only two measurements. Although the ESH recommendations state that at least two measurements should be obtained, they also emphasise that repeated measurements should be performed if there is uncertainty or distraction²¹. Moreover, our data clearly show that the first measurement is always significantly higher than subsequent ones. This implies that the average of a second and a third reading are more likely to yield a stable BP value than when the first two measurements are averaged.

It may seem that our recommendation for five days of measurement may create too large a burden for patients. However, this measurement procedure only has to be performed when a decision about starting or changing antihypertensive therapy is needed or when it is essential to exactly know a patient's BP as e.g. in some elderly subjects or in diabetics. Otherwise, a minimum measurement of one week per quarter may suffice²³. Additionally, discarding the first two days of measurement and the first measurement of each session may seem a waste of time and measurements for patients and practitioners. However, due to an increased cuff response, values are deviating from subsequent values and therefore may disturb reproducibility of BP data.

As already shown by other studies the effect of adaptation highly influences readings and should, therefore, not be underestimated¹³. Since the cuff response seems to diminish when patients measure their BP more frequently, discarding the first measurements may not be necessary anymore after several SBPM sessions have been performed and the patient is familiar with the procedure.

Discarding measurements of the first days as well as discarding first measurements of each triplicate session leads to lower BP values. For that reason, one may have to consider to establish new (lower) reference values, which should be determined according to the risk of developing cardiovascular disease in the future. Although this is complicated and very time-consuming, we may have to pursue this as it is the only way to determine precisely the predictive value of SBPM.

How should our results be interpreted in the light of existing recommendations concerning SBPM? Although the guidelines of the European Society of Hypertension clearly state that at the time no study had analysed the optimal timing and frequency of measurements²¹, it was proposed to follow the recommendations of the German Hypertension League²³. Although the number of measurements in our study was slightly greater, by and large our data confirm the validity of those recommendations. Therefore, we now provide the evidence which was previously lacking. Nevertheless, we add new information concerning the impact of gender, age and the height of office blood pressure. This information should, therefore, be considered in future adaptations of the guidelines.

In conclusion, the minimum number of SBPM necessary to obtain a BP value that correlates best with ABPM is five days of measurement. Each day, three consecutive morning and evening measurements should be performed and the first two days and the first measurement of each triplicate session may have to be discarded. For women, on the other hand, it may be sufficient to perform morning measurements only.

References

1. Stergiou GS, Zourbaki AS, Skeva, Il, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *Am J Hypertens* 1998;11:820-7.
2. Omvik P, Gerhardsen G. The Norwegian office-, home-, and ambulatory blood pressure study (NOHA). *Blood Press* 2003;12:211-9.
3. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 2002;25:2218-23.
4. Mule G, Caimi G, Cottone S, Nardi E, Andronico G, Piazza G, Volpe V, Federico MR, Cerasola G. Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk* 2002;9:123-9.
5. Shimada K, Kario K, Umeda Y, Hoshida S, Hoshida Y, Eguchi K. Early morning surge in blood pressure. *Blood Press Monit* 2001;6:349-53.
6. Tsunoda S, Kawano Y, Horio T, Okuda N, Takishita S. Relationship between home blood pressure and longitudinal changes in target organ damage in treated hypertensive patients. *Hypertens Res* 2002;25:167-73.
7. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Luscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 2003;21:1779-86.
8. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328:634-40.
9. Celis H, De Cort P, Fagard R, Thijs L, Staessen JA. For how many days should blood pressure be measured at home in older patients before steady levels are obtained? *J Hum Hypertens* 1997;11:673-7.
10. Garcia-Vera MP, Sanz J. How many self-measured blood pressure readings are needed to estimate hypertensive patients' "true" blood pressure? *J Behav Med* 1999;22:93-113.
11. Liabre MM, Ironson GH, Spitzer SB, Gellman MD, Weidler DJ, Schneiderman N. How many blood pressure measurements are enough? An application of generalizability theory to the study of blood pressure reliability. *Psychophysiology* 1988;25:97-106.
12. Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsumi K, Satoh H, Imai Y. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004;22:1099-104.
13. Stergiou GS, Skeva, Il, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? *J Hypertens* 1998;16:725-31.
14. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997;29:22-9.
15. Verdecchia P, Clement D, Fagard R, Palatini P, Parati G. Blood Pressure Monitoring. Task force III: Target-organ damage, morbidity and mortality. *Blood Press Monit* 1999;4:303-17.
16. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;348:2407-15.
17. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, De Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999;282:539-46.
18. Verdecchia P, Reboldi G, Porcellati C, Schillaci G, Pede S, Bentivoglio M, Angeli F, Norgiolini S, Ambrosio G. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J Am Coll Cardiol* 2002;39:878-85.

19. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
20. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *Blood Press Monit* 1996;1:55-61.
21. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P, on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48.
22. Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman & Hall 1993.
23. Mengden T, Chamontin B, Phong Chau N, Luis Palma Gamiz J, Chanudet X. User procedure for self-measurement of blood pressure. First International Consensus Conference on Self Blood Pressure Measurement. *Blood Press Monit* 2000;5:111-29.

Chapter 6

Masked hypertension is not a discrete entity but a result of the moment

Abstract

Context

Masked hypertension (MH) is considered to be a patient characteristic but it has never been investigated whether it is persistent on repeated measurements.

Objective

To investigate whether MH is a discrete, hence persistent, entity or the result of an accidentally deviating blood pressure (BP) at a particular moment.

Design, settings and participants

One hundred sixty-three mild-to-moderate hypertensive patients with a mean age of 56 years (56% males) had office blood pressure measurements (OBPM) at eight visits (3 readings per visit) and performed self blood pressure measurements (SBPM) for one week prior to each visit (42 readings per week) over a period of one year. All measurements were performed with the same automatic device (Omron HEM-705CP).

Main outcome measures

At each visit, MH was determined according to three definitions: the ESH definition (OBPM < 140/90 mmHg and SBPM $\geq$ 135 mmHg and/or 85 mmHg), the 5/3 definition (SBPM is 5 mmHg systolic and 3 mmHg diastolic higher than the OBPM) and the 10/6 definition (SBPM is 10 mmHg systolic and 6 mmHg diastolic higher than OBPM).

Interventions

At the start, patients were untreated. Thereafter, treatment was based on the SBPM values.

Results

Considering all eight episodes of BP measurement, 40% of the patients had at least once MH according to the ESH and 5/3 definition. Commonly, MH was caused by rather low OBPM values at one occasion. At four sequential OBPM visits only 1% had MH according to all definitions. The prevalence of MH was higher with lower OBPM levels when the ESH definition was applied, but remained constant with the 5/3 and 10/6 definitions.

Conclusions

MH is not a persistent patient characteristic, but usually results from an accidentally low OBPM value at one particular occasion.

Introduction

Several lines of evidence indicate that conventional office blood pressure measurement (OBPM) alone is not sufficient to estimate a patient's usual blood pressure (BP). Reasons are that BP is extremely variable, measurements performed with a manual sphygmomanometer are subject to observer bias¹, and above all, in many patients a white coat effect (WCE)² is observed. Recently, another phenomenon that contributes to the unreliability of OBPM has attracted attention: masked hypertension (MH)³, also known as reverse white coat hypertension⁴ or white coat normotension. A patient is considered to have MH if his or her BP is normal in the clinic and elevated if measured outside the doctor's office⁵. The underlying mechanism is not completely understood although it may be related to cigarette smoking⁴ or to a highly active daily life³. Since epidemiological evidence indicates that these patients are at increased risk for developing cardiovascular events in the future, a reliable diagnosis of MH is essential^{6,7}.

Thus far, it remains uncertain whether MH is a discrete entity that should be given special attention for want of antihypertensive treatment, or that it is the result of accidentally low OBPM and high SBPM (or daytime ABPM) values at one particular occasion. To address this issue, we performed the present study to assess the persistence of MH during repeated measurements in hypertensive patients who were on drug treatment and on supervised follow-up for a period of one year.

Methods

Patients participated in the HOMERUS-trial of which the design has been described in detail elsewhere⁸. In brief, 430 patients were recruited from the outpatient departments of four participating hospitals and from general practices surrounding these centres of which 216 patients performed SBPM. Both previously treated and untreated patients with essential hypertension qualified for inclusion. The duration of the trial was one year during which OBPM and SBPM data were obtained at eight visits. At entry into the study, any existing antihypertensive therapy was discontinued whenever possible and patients entered a placebo run-in period of four weeks duration, before study treatment was initiated. Consequently, patients were on antihypertensive treatment during seven of the eight measurement sessions. Based on the SBPM results, medication was adjusted according to a stepwise treatment schedule after each visit. Target SBPM values were set at 120-140 mmHg systolic and 80-90 mmHg diastolic. Lower pressures would lead to a dose reduction. All treatment decisions were taken at the coordinating centre so that both the doctor and the patient were blinded for the medication. Laboratory

assessments were performed at the end of the run-in period and at the end of the trial. All patients gave their informed consent and the study was approved by the ethics committees of all participating centres before inclusion of patients into the study.

Blood pressure measurements

At every visit, three consecutive OBPMs were performed in the hospital or at the general practitioners clinic. SBPM was done six times a day (three readings in the morning and three in the evening) for a 7-day period, prior to every visit. Patients were requested to register their self-measurements on a form and to print out each measurement. The SBPM value was determined from the average of the 42 measurements. Both OBPM and SBPM were always performed at the non-dominant arm in sitting position after at least five min of rest, using the same fully automated validated Omron HEM-705CP device .

Laboratory analyses

Blood was drawn from fasting patients for determination of blood glucose, serum cholesterol (total and HDL-cholesterol) and serum creatinine. Urinary (micro-) albumin concentrations were assessed from two consecutive 24-h urine collections. All micro-albumin measurements were performed in the same laboratory.

Definitions of masked hypertension

At each visit the number of patients with MH was determined according to three separate definitions. The first definition follows the ESH guidelines⁹ which state that MH is present when OBPM values are lower than 140 mmHg systolic and 90 mmHg diastolic while the SBPM value is equal to or greater than 135 mmHg systolic and/or 85 mmHg diastolic. The second one describes MH as a condition in which the SBPM value is, at least, 5 mmHg systolic and 3 mmHg diastolic higher than the OBPM value: the 5/3 definition. The third one is similar as the second one but with SBPM values which are, at least, 10 mmHg systolic and 6 mmHg diastolic higher than the OBPM values: the 10/6 definition. Differences in mean BP values between one visit and another were analysed with the Student t-test using SPSS version 12.0 (SPSS, Inc. Chicago, Illinois). A p -value <0.05 was considered significant (2-sided).

Results

Of the 216 patients who were included in the trial, 19 did not complete the study because they withdrew consent ($n=18$) or had an adverse event ($n=1$). Another 34 patients were not included in the analysis either because their previous treatment could not be stopped ($n=10$) or because they missed one follow-up visit or skipped one SBPM session prior to a visit ($n=24$). These 53 patients did not differ from the remaining 163 patients whose characteristics are presented in Table 6.1. On average, patients performed 39 ± 4 of 42 predetermined SBPMs.

Table 6.1 Distribution of clinical characteristics at inclusion.

Parameter	($n=163$)
Males, n (%)	91 (55.8)
Age, yr (SD)	55.7 (10.0)
BMI, kg/m^2 (SD)	27.7 (4.4)
Smoking, n (%)	30 (18.4)
Alcohol, n (%)	126 (77.3)
Glucose, mmol/l (SD)	5.4 (0.9)
Cholesterol, mmol/l (SD)	5.7 (1.0)
Creatinine, $\mu\text{mol/l}$ (SD)	82.5 (14.5)
Microalbuminuria, mg/24-h (IQR) ^a	10.0 (6-20)
Number of patients on previous antihypertensives, n (%)	
0, n (%)	49 (30.1)
1, n (%)	66 (40.5)
2, n (%)	36 (22.1)
3 or more, n (%)	12 (7.3)

BMI indicates body mass index; ^a results are given as median. IQR interquartile range

BP and heart rate values for all eight visits throughout the trial are illustrated in Table 6.2. BP fell with every visit and at all visits average SBPM values were lower than the corresponding OBPM values.

Figure 6.1 shows the relationship between OBPM and SBPM values for all patients at the end of the run-in period (left panel), when subjects were still untreated, and at the end of the trial (right panel) when they were using antihypertensive drugs.

Table 6.2 Blood pressure and heart rate values (mean ± SD) at eight visits of the trial.

	OBPM mean (SD)			SBPM mean (SD)		
	SBP (mmHg)	DBP (mmHg)	HR (beats/min)	SBP (mmHg)	DBP (mmHg)	HR (beats/min)
Months						
0	165 (19)	96 (9)	77 (12)	155 (18)	92 (9)	71 (8)
1	155 (21)	92 (11)	78 (11)	145 (18)	86 (9)	70 (8)
2	153 (21)	91 (10)	75 (11)	142 (16)	85 (9)	70 (8)
4	149 (19)	88 (10)	76 (11)	137 (13)	82 (8)	70 (9)
6	144 (16)	85 (9)	75 (12)	136 (10)	81 (6)	69 (9)
8	144 (16)	85 (9)	76 (13)	135 (10)	81 (7)	69 (9)
10	143 (17)	84 (9)	76 (12)	134 (10)	80 (6)	69 (10)
12	143 (17)	84 (9)	75 (12)	133 (9)	80 (6)	69 (9)

OBPM indicates office blood pressure measurement; SBPM, self blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

Figure 6.1 Systolic and diastolic blood pressure for patients without antihypertensive treatment (untreated) at the end of a 4-week run-in period and at the end of the trial when patients were among antihypertensive treatment (treated). The dashed vertical and horizontal lines depict the target limits for office (OBPM) and self blood pressure measurement (SBPM). The dashed and continuous diagonal lines illustrate that SBPM is 5 mmHg or 10 mmHg systolic or 3 mmHg or 6 mmHg diastolic higher than OBPM, respectively.

This graph clearly illustrates that the ESH definition tends to overestimate MH since it classifies patients as having MH who have almost comparable BP values for SBPM and OBPM. The figure also demonstrates that the number of patients who are classified as being masked hypertensive is likely to increase when the population is shifted to the left lower quadrant after drug treatment. On the contrary, when a masked hypertensive effect is considered such as is implied by the 5/3 and the 10/6 definitions, the prevalence of MH remains rather stable. This is further supported by the data from Figure 6.2 which shows for each visit the proportion of patients who were diagnosed with MH according to the three different definitions. While the prevalence of MH increased during the trial (when BP fell due to the treatment) according to the ESH definition, it remained rather stable when the 5/3 and 10/6 definitions were applied.

Figure 6.2 Percentage of patients who were classified as being masked hypertensive at each visit according to three definitions: ESH (■), 5/3 definition (▲) and the 10/6 definition (●). The straight line indicates the regression line for the ESH definition ($r=0.74$; $p<0.05$), the dashed line belongs to the 5/3 definition ($r=0.02$; ns) and the dotted line to the 10/6 definition ($r=0.03$; ns).

The proportion of patients who were found to have MH at more than one occasion fell with the number of visits. According to the ESH definition, over 45% of all patients were at least once classified as having MH definition but merely half of them also had MH a second time during the trial (Figure 6.3, left panel). Only a very small percentage of patients had MH at more than five visits and in none of the subjects MH persisted for more than six visits. Similar trends were observed with respect to the other definitions of MH. Since there was little overlap in the occurrence of MH between visits (on average 24, 25 and 30% respectively with the ESH, 5/3 and 10/6 definitions), it follows that most patients who were labelled as having MH at one visit did not have the condition at the next one (Figure 6.3, right panel). Indeed, very few patients had MH for three or more consecutive visits and less than 2% of all patients had MH at four or more subsequent occasions.

Figure 6.3 Percentage of patients in whom masked hypertension (MH) persisted over time. Left panel: prevalence when any visit is being considered. Right panel: persistence of MH during consecutive visits. MH was diagnosed according to three different definitions: the ESH □, 5/3 ■ and 10/6 ■ definition (see methods).

In an attempt to elucidate why patients had masked hypertension at one but not at the next occasion, all BP data from these cases were studied in more detail. In Figure 6.4 we have plotted the individual differences in OBPM values between the visit at which MH was diagnosed and the next visit against the corresponding differences in SBPM. As the graphs show, most data points cluster below the X-axis indicating that patients usually had a lower OBPM value at the visit when MH was diagnosed than at the next visit. For SBPM this was opposite with higher values at the time of MH but lower thereafter.

Figure 6.4 Mean systolic and diastolic office blood pressure measurement (OBPM) and self blood pressure measurement (SBPM) values for each patient classified as masked hypertensive at one visit but not at the next according to three definitions: the 5/3, 10/6 and ESH definition.

These trends were seen with all three definitions of MH which we used. Finally, in Figure 6.5 the average differences for the whole group are presented.

Figure 6.5 Mean systolic and diastolic office blood pressure measurement (OBPM) and self blood pressure measurement (SBPM) values from patients who were classified as masked hypertensive at one visit but not at the next visit according to three definitions: the ESH, 5/3 and 10/6 definition. (□) indicates the visit where masked hypertension was diagnosed; (■), the next visit; ***, a $p < 0.001$; **, $p < 0.005$ and *, $p < 0.01$. Values are depicted as mean $\pm$ SEM.

Discussion

Our findings show that at eight consecutive visits, 45% of all patients were at least once classified as having MH according to the ESH and 5/3 definition. Usually, MH was the result of an occasionally low OBPM value at one visit. Moreover, only a small proportion of patients exhibited MH at multiple

occasions but even then most often not at consecutive visits. Despite the fact that MH, at least in terms of the ESH definition, led to an escalation of antihypertensive treatment, OBPM values were commonly increased and SBPM (as expected) reduced at the visit following the occasion when MH was diagnosed. In the end, only 1% of all patients had MH at four subsequent visits according to the ESH and 10/6 definitions and 2% according to the 5/3 definition. Importantly, in our study both OBPM and SBPM were performed with the same automatic device which rules out measurement errors due to different devices or observer bias as the cause of the divergent results.

Although the ESH definition of MH has been commonly accepted, it has some important limitations. First of all, patients can be classified as having MH when they have equal OBPM and SBPM values. For instance, a subject who has a BP of 138/88 mmHg both in the office and at home meets the ESH criteria of MH even though nothing is masked. Secondly, the ESH definition only detects patients with BP values around the upper limits of normality and ignores those who have a marginally elevated pressure in the office but a substantially higher pressure at home. Especially this latter group of patients may require more attention as even small increases in usual pressure are associated with an enhanced risk of cardiovascular complications¹⁰. For these reasons, we adopted two other definitions to diagnose masked hypertension or, for that matter, a masked hypertensive effect, namely the 5/3 and 10/6 definitions. Epidemiological evidence supports the relevance of these values: each 5 mmHg increment in systolic pressure increases the risk of stroke by 18 to 30% and that of cardiovascular events by 9 to 18%^{11,12}. An increased diastolic BP of 5 to 6 mmHg even enhances the risk of stroke by 35 to 40%, of coronary heart disease by 20 to 25% and that of all cardiovascular events by 12%^{6,10,13,14}.

Because the ESH definition is based on BP levels which are close to normal, it is not surprising that the prevalence of MH was higher as OBPM levels were lower. However, prevalences according to the 5/3 and 10/6 definitions remained rather constant. Hence, there is a case to use one of these latter definitions because these are not only applicable at any BP level but also provide more clinically relevant information about a patient's BP status.

Although MH has just recently become a topic of interest, several studies have already addressed this issue in some detail. Data obtained in several cross-sectional studies have demonstrated huge differences in the prevalence of MH varying from 8% in a general population to 49% in transiently hypertensives¹⁵. It is also seen in children and young adults (11%)¹⁶ and may be as common as white coat hypertension¹⁷. Patients with MH had comparable degrees of target organ damage^{18,19} and similar cardiovascular prognosis as true hypertensives⁶. This suggests that patients with masked and sustained hypertension are not fundamentally different from each other but rather represent a different phenotypic expression of high BP.

A few studies have evaluated the reliability of SBPM for detecting MH. For instance, Stergiou *et al.* have shown that SBPM is as reliable as ABPM for the diagnosis²⁰. According to Mallion *et al.* three measurements at two visits for OBPM and three measurements in the morning and in the evening over two days for SBPM are required to diagnose MH²¹. However, none of these studies have investigated whether MH is reproducible on repeated testing.

In the interpretation of the results of our study some limitations should be taken into account. First of all, patients were treated on the basis of their SBPM results. This means that most patients with MH received intensified treatment, which may have prevented them from having MH at the next occasion since the SBPM value usually was reduced then. However, most of these patients showed a higher OBPM value at the next visit despite increased treatment. Probably, their OBPM value would have been even higher if drug therapy had not been uptitrated. This is further corroborated by the fact that according to the 5/3 and 10/6 definition the number of patients with MH remained constant throughout the trial suggesting that as such the MH effect is independent of antihypertensive treatment or BP level. Secondly, during the follow-up period all patients were receiving antihypertensive treatment and they could have taken their drugs just a few hours before OBPM was performed. This would have increased their chance of being diagnosed as masked hypertensive. Finally, our patients had mild to moderate hypertension and, therefore, our data cannot a priori be extrapolated to other populations.

Thus far, MH has been studied among both untreated and treated patients. As a matter of fact, however, hypertension can hardly be considered as masked when patients are treated for their disease. This means that consensus is needed about the question whether we should look for masked hypertension (by definition, in untreated subjects only) or for a masked hypertensive effect which certainly is not a persistent phenomenon as the present study shows. Although our data indicate that antihypertensive treatment does not necessarily influence the occurrence of MH, it seems recommendable to perform a long-term follow-up study with repeated measurements in a general population without antihypertensive treatment.

Taken all results together, we conclude that MH is not a discrete clinical entity but rather a common yet fortuitously occurring phenomenon which may be attributed to an exceptionally low OBPM value at one particular occasion. This finding justifies the implementation of SBPM into clinical practice in order to detect MH. Finally, we recommend that the ESH definition for MH be redefined since it only concentrates on patients with BP values around the upper limits of normal while the masked hypertensive effect itself is of clinical and epidemiological importance at all levels of BP.

References

1. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
2. Stergiou GS, Zourbaki AS, Skeva, II, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *Am J Hypertens* 1998;11:820-7.
3. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002;40:795-6.
4. Wing LM, Brown MA, Beilin LJ, Ryan P, Reid CM. 'Reverse white-coat hypertension' in older hypertensives. *J Hypertens* 2002;20:639-44.
5. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the subcommittee of professional and public education of the american heart association council on high blood pressure research. *Circulation* 2005;111:697-716.
6. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342-9.
7. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsumi K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005;46:508-15.
8. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
9. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;23:697-701.
10. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
11. Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. *J Hypertens* 2003;21:1055-76.
12. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999;282:539-46.
13. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
14. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827-38.
15. Palatini P. Masked hypertension: how can the condition be detected? *Blood Press Monit* 2004;9:297-9.
16. Matsuoka S, Awazu M. Masked hypertension in children and young adults. *Pediatr Nephrol* 2004;19:651-4.

17. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. In clinical practice, masked hypertension is as common as isolated clinic hypertension: predominance of younger men. *Am J Hypertens* 2005;18:589-93.
18. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999;131:564-72.
19. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation* 2001;104:1385-92.
20. Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? *Am J Hypertens* 2005;18:772-8.
21. Mallion JM, Genes N, Vaur L, Clerson P, Vaisse B, Bobrie G, Chatellier G. Detection of masked hypertension by home blood pressure measurement: is the number of measurements an important issue? *Blood Press Monit* 2004;9:301-5.

Chapter 7

Masked hypertension, a review of the literature

Abstract

Masked hypertension (blood pressure that is low in the physician's office but elevated elsewhere) is a common phenomenon as prevalence among studies varies from 8 to 45% and is seen at all ages. However, there are large discrepancies between studies that dealt with masked hypertension. It is of high clinical importance as it is associated with higher target organ damage as compared to sustained normotension. Therefore more research should be performed to masked hypertension; consensus should be reached on its definition and how it should be determined. This paper provides an overview of current literature and aims at revealing obscurities among masked hypertension. In addition it provides some questions, which need to be answered for performing appropriate research to this subject in future

Introduction

Several lines of evidence indicate that office blood pressure measurement (OBPM) alone is not sufficient to estimate a subject's "true" blood pressure as a risk factor. For that reason, ambulatory blood pressure measurement (ABPM) or self-measurement of blood pressure at home (SBPM) should be performed in addition to OBPM. However, when discrepancies are found between OBPM and SBPM or ABPM, interpretation of the data becomes complicated. White coat hypertension (a condition in which an individual is hypertensive by OBPM but normotensive by ABPM or SBPM) and the white coat effect (an OBPM value which is higher than the SBPM or ABPM value) have already been investigated extensively but the opposite effect (a subject is normotensive by OBPM but hypertensive by ABPM or SBPM) has received less attention.

This phenomenon, which previously was referred to as "reverse white-coat hypertension", "white coat normotension", "isolated home hypertension" or "Isolated ambulatory hypertension" has now been given the more appropriate name "masked hypertension"¹. Since masked hypertension seems to be a common phenomenon, it is fully justified to give it more attention.

According to international guidelines, masked hypertension is defined as an OBPM value <140/90 mmHg and a daytime ABPM or SBPM value $\geq$ 135 mmHg systolic and/or 85 mmHg diastolic².

This reviews deals with several aspects of masked hypertension such as its prevalence, its relation to target organ damage, cardiovascular prognosis and associated patient characteristics.

Prevalence of masked hypertension

Many studies have addressed the prevalence of masked hypertension³⁻¹⁹ (Table 7.1). However, heterogeneity among the studies with respect to methodology, blood pressure, cut-off points etcetera led to large differences in prevalence (from 8 to 45%) and makes it difficult to interpret the data.

The available studies included a wide range of study groups such as a general population^{3,6,15}, normotensives^{10,18} untreated hypertensives¹⁶, treated hypertensives^{13,19}, normotensives and hypertensives^{4,7,11} patients referred to a hypertensive clinic^{12,14} but also diabetics⁵, children and adolescents^{7,10,12} elderly^{5,6,8,13,19} or only males^{6,17}. Probably even more relevant is that there were also differences in the methodology of OBPM: in a few studies OBPM was performed with an automatic oscillometric device^{15,18} whereas a mercury sphygmomanometer was used in the remainder. Sometimes a nurse or technician^{4,7,11,19} rather than a physician performed OBPM. When assessed by a technician or a nurse OBPM data tend to be lower than when measured by a

physician²⁰, and this alone may lead to overestimation of the masked hypertension prevalence. Whereas in most studies, OBPM was performed in the sitting position some were done in the supine position^{6,16}. Since blood pressure values fluctuate with changing body position²¹, the prevalence on masked hypertension may also depend on posture.

The great diversity among blood pressure thresholds also leads to differences in prevalence as was illustrated by Poncelet *et al.*⁹. In addition, Mallion *et al.* found with data from the SHEAF study that the number of blood pressure measurements also affects prevalence. Varying the number of measurements for both OBPM (from 3 to 6 measurements) and SBPM (from 3 to 15 measurements) changed the prevalence of masked hypertension from 8.9 to 12.1%²². Another factor that complicates the comparison between studies is that some studies used either ABPM^{4,6,7,10-12,15-19} or SBPM^{5,8,9,13} or both methods^{3,14} to assess the existence of masked hypertension.

From a more practical point of view, one can speak of masked hypertension only when the patient is untreated because, when treated, the hypertension is not masked anymore.

Nevertheless, also the lack of treatment effect may be masked when blood pressure is normal in the office and elevated outside. It is not surprising, therefore, that the current literature on masked hypertension comprises studies on both untreated and treated patients. Since it is unlikely that the mechanisms which lead to the discrepancy between office and home blood pressure are fundamentally different for treated and untreated individuals, it is reasonable to consider masked hypertension as a characteristic feature which is independent of treatment status.

Self and ambulatory blood pressure measurement

Although ABPM and OBPM have in common that they provide multiple blood pressure measurements outside the clinic, there are some important differences between these two methods. SBPM is often measured on different days and with the patient at rest. ABPM, on the other hand, comprises measurements during one whole day including periods of physical activity and sleep. Studies, which assessed masked hypertension, have utilised both 24-h and daytime ABPM values, although more often daytime values were used. Intuitively, daytime ABPM is to be preferred in this regard.

Using data from the Pamela study Segal *et al.* found similar prevalences of masked hypertension with daytime ABPM and SBPM. In addition, two-thirds of the patients identified as having masked hypertension based on ABPM also had masked hypertension based on SBPM³. Stergiou *et al.* also investigated the level of agreement between ABPM and SBPM in the diagnosis of masked

hypertension¹⁴. Among 438 treated and untreated subjects referred to a hypertension clinic, similar proportions of subjects with masked hypertension were diagnosed by daytime ABPM (14.2%) and SBPM (11.9%). However, in the 132 subjects with normal OBPM, there was disagreement between the methods in 23% of subjects for systolic and 30% for diastolic blood pressure. However, when a 5-mmHg grey zone for uncertain diagnosis was applied to the diagnostic threshold (that was considered as clinically relevant), the disagreement was reduced to 9% and 6% respectively. Therefore, both ABPM and SBPM are appropriate methods for the detection of masked hypertension.

Clinical impact of masked hypertension

The presence of masked hypertension is associated with more target organ damage (heart, kidney) as compared to that in sustained normotension and similar to that in sustained hypertension^{4,5,7,23}. A study of Segá *et al.* showed that left ventricular wall thickness, and the prevalence of LVH were less in masked hypertensives than in sustained hypertensives but greater than in sustained normotensives³.

Several long-term follow-up studies have provided data, which allow assessing the prognosis of subjects with masked hypertension. Most of these found that masked hypertension is associated with a 2 to 3-fold increased risk of cardiovascular morbidity and mortality^{6,8,15} and stroke morbidity¹⁵ as compared to that in sustained normotensives, but with a similar risk as that of sustained hypertensives. In addition, masked hypertension subjects had a 2-fold increased risk to develop sustained hypertension and to need antihypertensive medication as compared to sustained normotensives¹⁶.

In contrast, Lurbe *et al.* found among 34 masked hypertensive children and adolescents that after 3-year of follow-up 18 subjects became normotensive, 13 had persistent masked hypertension and only three had sustained hypertension⁷.

Taken the available data together, it seems that masked hypertension is not an innocent phenomenon but carries a prognosis that is at least close to that of patients with sustained hypertension. This raises the question whether masked hypertension should not be considered as a peculiar phenotypic variant of true hypertension, which is perhaps characterised by somewhat greater variability of pressure.

Table 7.1. Studies on the prevalence of masked hypertension

Ref	Population	N	Age (y)	Men (%)	Readings	OBPM			SBPM			ABPM			Masked Hypertensives N(%)
						Days	Threshold (mmHg)	Readings	Days	Threshold (mmHg)	ABPM (intervals) (min)	Threshold (mmHg)			
3	General Population	1631 1522	25-74	58	3	1	<140/90	3M, 3E	1	≥132 or 83	20	≥125 or 79 (24-h)		132 (9)	
4	NT & HT stage1	359	33-66	?	≥2 Supine	≥2 ^a (Nurse)	<140/90				Day: 15 Night: 30	≥134 or 90 (Day)		140 (9) 61 (17)	
5	DM2	148	70	45	1	6	<140			≥135				49 (33)	
6	General Population	578	70	100	2	1	<140/90	1M	14-21		Day: 20 Night: 20/30	≥135 or 85 (Day)		82 (14)	
7	NT & HT	592	6-18	44	3	1	<95th	Supine			Day: 20 Night: 30	≥95th (24-h)		45 (8)	
8	HT 95% Treated	4939	70	49	3	2	<140/90	3M, 3E	4	≥135 or 85				462 (9)	
9	?	575	?	?	3	1	SBP <140 <135 DBP <90 <85 <140/90 <135/85	3M, 3E	4	SBP ≥135 ≥135 DBP ≥85 ≥85 ≥135 or 85 ≥135 or 85			112 (19) 127 (22) 117 (20)		
10	NT NT	103 23	6-15 16-25	45 40	1	3	<95th (≤18y) <140/90 (>18y)				Day: 30 Night: 60	≥95th (≥15y; Day) ≥135 or 85 (>15y; Day)		44(11) 78 (14) 61 (11) 11 (11) 4 (12)	
11	NT & HT 67% Treated	1494	58	44	2 to 3	1(Nurse)	<140/90				?	≥135 or 85 (Day)		53 (11)	
12	Referred to HT clinic	85	14	59	3	1 ^a	<95th				15	≥95th (Day)		8 (9)	
13	HT Treated	3400	66	45	2	1	<140/90	1M	14	≥135 or 85				777 (23)	
14	Referred to HT clinic	438	52	59	2	3 ^a	<140/90	2M, 2E	6 ^b	≥135 or 85				52 (12)	
15	34% Treated														
16	General population	1332	61	40	2 AOD	1(Nurse)	<140/90				20	≥135 or 85 (Day)		62 (14)	
17	HT Untreated	871	33	74	2 Supine	3	<140/90				30	≥135 or 85 (Day)		221 (17)	
18	HT & NT	267	30-60	100			DBP <85				30	> 85 DBP (Day)		120 (14)	
18	NT	319	17-68	50	5	1	SBP <140 DBP <90				8-10h 20	≥135 SBP ≥ 90 DBP (Day)		36(13) (23) (24)	
19	HT Treated	713	65-83	53	3	3	SBP: ABPM>OBPM DBP: ABPM>OBPM				26h 30	SBP: ABPM>OBPM DBP: ABPM>OBPM		(21) (45)	

OBPM indicates office blood pressure measurement; SBPM, self blood pressure measurement; ABPM, ambulatory blood pressure monitoring; N, number of patients; HT, hypertension; NT, normotension; M, morning readings; E, evening readings; DM2, Diabetes Mellitus type 2. AOD, automatic oscillometric device; SBP, systolic blood pressure; DBP, diastolic blood pressure; ?, not specified; ^a, the average blood pressure value was determined without the initial visit; ^b, the average self blood pressure value was determined without the readings of the initial day. Office readings were taken in the sitting position with a mercury sphygmomanometer by a physician unless otherwise mentioned. Ambulatory blood pressure measurements were taken for 24 h unless otherwise mentioned.

Patient characteristics of masked hypertensives

It would certainly be helpful when subjects with masked hypertension could be recognised by certain characteristics. Although there is no uniform profile of a patient with masked hypertension, such patients are more often male^{11,18,24} and have a higher BMI or waist-to-hip ratio^{4,6,19}. In addition, they are more often smokers^{4,18,19,24}, consume more alcohol^{13,18} and use antihypertensive drugs^{5,13,14}. Some studies also found a higher prevalence of subjects with previous antihypertensive treatment¹⁹, a history of cardiovascular disease²⁴ a higher heart rate¹¹ and a relative higher systolic blood pressure value as compared to normotensives¹³ but these observations have not always been confirmed. Some studies found a higher masked hypertension prevalence in older subjects^{4,18} whereas others found the opposite^{25,26}. Studies that investigated the prevalence of masked hypertension in children and young adults^{7,10,12} reported prevalences of 8-12%, which is quite similar to the prevalence of masked hypertension among adults.

Masked hypertension in children

Thus far, only three studies have addressed the issue of masked hypertension among children and adolescents^{7,10,12}. These studies all used ABPM as an out-of-office measurement, which is also in paediatric patients emerging as a valuable tool in the assessment of white coat hypertension, the white coat effect and masked hypertension¹⁰.

All studies showed that masked hypertension is present in paediatric patients, more commonly in boys than in girls (19% vs. 5%)¹⁰. In the study of Stabouli *et al.*¹² masked hypertension was only diagnosed in non-obese children whereas white coat hypertension was more prevalent among obese children. This is in contradiction with the results of Lurbe *et al.* who noticed that masked hypertensive subjects are more obese⁷.

Children with masked hypertension have a significantly higher left ventricular mass index than normotensives^{7,12} and are 2.5 times more likely to have a parental history of hypertension⁷.

Lurbe *et al.* are the only ones who assessed the persistence of masked hypertension. They found that from 34 subjects with masked hypertension, 13 subjects still had masked hypertension after 37 months follow up, three developed sustained hypertension and 18 became normotensive⁷.

Comment

The prevalence of masked hypertension varies from 8 to 45%, which illustrates that masked hypertension is at least a common phenomenon. SBPM is a reliable tool to detect masked hypertension, it gives the same prevalence as ABPM and the level of agreement between ABPM and SBPM is about 70%. However, when differences between OBPM and SBPM or ABPM smaller than 5 mmHg are omitted, agreement increases to over 90%. Masked hypertension is associated with more organ damage as compared to sustained normotensive subjects and commonly, the degree of organ damage is similar to that in sustained hypertension. Just as those with sustained hypertension subjects with masked hypertension have a 2 to 3-fold higher risk of cardiovascular morbidity and stroke than sustained normotensives. Masked hypertensive subjects were often characterised as being male, and having a high BMI, a higher prevalence of smokers and habitual drinkers and users of antihypertensive treatment. Finally, in children and adolescents masked hypertension prevalence ranges from 8 to 12% and is a precursor of sustained hypertension and left ventricular hypertrophy¹².

ABPM and SBPM are better risk predictors than OBPM

Since ABPM and SBPM give a better classification of risk than OBPM²⁷⁻³³, one may be inclined to regard masked hypertensives as actually being sustained hypertensives. This is supported by several studies which demonstrated an abnormal ABPM or SBPM in the presence of normal OBPM is associated with a higher prevalence of cardiovascular morbidity and mortality^{6,8,15,24,33}. However, there still exists a positive correlation between OBPM and cardiovascular risk^{34,35}. In addition, some studies that evaluated the long-term effects of white coat hypertension (a normal ABPM or SBPM and an elevated OBPM) on cardiovascular prognosis showed that subjects with white coat hypertension had an increased risk as compared to normotensives, but a lower risk than those with sustained hypertension³⁶. These data indicate that the OBPM values should not completely be ignored.

The threshold effect (patients closer to threshold are more likely to have masked hypertension)

A limitation of the definition of masked hypertension² is that only patients qualify for diagnosis who have blood pressure values around the upper limits of normal pressure. As Selenta *et al.*¹⁸ showed in half the subjects with BP values within 10 mmHg above or below the 140/90 mmHg OBPM limit, the diagnosis according to OBPM, proved to be incorrect. This may partly explain why

masked hypertensive patients sometimes have lower OBPM and ABPM or SBPM values and thus lower degrees of target organ damage than patients with sustained hypertension⁶.

Since patients with stage I hypertension have the greatest chance of being classified as having masked hypertension, guidelines indicate that these subjects should be followed for at least 2 months before deciding whether they need antihypertensive treatment or not³⁷.

In order to reveal whether the effect, which causes masked hypertension, is also seen in patients with higher BP values one could consider introducing a so-called masked hypertension effect. The magnitude of such an effect can be determined by subtracting the OBPM value from the daytime ABPM or SBPM value, or to set the limit for a masked hypertension effect as an SBPM or daytime ABPM value ≥ 5 mmHg than the OBPM value, as was proposed by Wing *et al.*¹⁹.

Explanation for masked hypertension

In order to explain masked hypertension most studies have addressed factors that increase daytime ambulatory blood pressure such as physical activity, stressful conditions, tobacco and coffee^{38,39}, alcohol⁴⁰, sedentary habits⁴¹ or greater reactivity to daily life stressors⁴². However, masked hypertension could, of course, also be due to an exceptional low OBPM in the face of increased SBPM or ABPM values. Firstly, some studies found a high number of patients on antihypertensive treatment among subjects on masked hypertension^{5,13,14,43}. This suggests that masked hypertension may be caused by the treatment as patients could have taken their medication a few hours before OBPM was performed. Alternatively, patients with poor adherence may have taken their drug the day before their visit to the physician's office. Secondly, many patients were measured once at a single visit, which is highly inaccurate. Therefore, the ESH guidelines recommend at least two measurements³². However, these guidelines only plead for more visits when increased blood pressures values are obtained and thus leave masked hypertensives undetected. Thirdly, most OBPMs were performed with a manual sphygmomanometer, which may easily introduce observer bias⁴⁴. Differences between trained observers can easily amount to 10 mmHg⁴⁵.

In addition, it is questionable whether physical activity alone can explain increased ABPM values since the prevalence of masked hypertension is similar when detected with SBPM, which are normally performed when the patient is at rest.

Older and younger subjects

Several hypotheses have been formulated to explain an increased prevalence of masked hypertensives among younger subjects. Firstly, the orthostatic effect, (the blood pressure response to standing), is more pronounced in young individuals or very elderly and is known to affect average daytime BP^{16,46-48}. Secondly, the relationship of ABPM data with age is less steep than that for OBPM and thus masked hypertension is less likely to appear in old individuals than in young subjects²⁶. Thirdly, masked hypertension is the opposite of white coat hypertension that is more frequently seen among older subjects. However, currently there are as many studies with a higher prevalence among younger subjects than there are studies that detected a higher prevalence among older subjects.

Reproducibility

Despite all studies about masked hypertension, little is known about the reproducibility of the classification of masked hypertension. Thus far, only two studies have more or less dealt with this subject. Lurbe *et al.* found in a paediatric population among 587 subjects that masked hypertension was persistent in roughly 50% of the cases⁷. Ben-Dov *et al.*¹¹ showed that among 82 subjects who underwent a second ABPM the prevalence of masked hypertension increased from 7 to 15 subjects with little overlap between the two measurements (four subjects had masked hypertension twice). A weakness of that study was that patients received treatment that was probably changed at the second measurement. So, in order to reveal the true identity of masked hypertension it is essential that more research is done to determine the reproducibility of masked hypertension.

Conclusion

All findings considered, we conclude the following: masked hypertension is a predictor of increased cardiovascular morbidity and mortality and associated with organ damage. Both SBPM and ABPM are appropriate methods to detect masked hypertension. Patients with blood pressure values within a 10 mmHg range of the defined threshold values for masked hypertension have the highest chance of being classified as masked hypertensive.

Future recommendations

This review clearly illustrates that very little is known about masked hypertension even though it seems a clinically significant phenomenon. Therefore, in order to expand our knowledge of masked hypertension more

research should be done, in particular with regard to its reproducibility, and consensus must be reached in how it should be detected. For this consensus several questions should be answered.

- 1) Which definition do we use? Will we hold on to the definition as made by the ESH?
- 2) How many OBPMs should be performed and in which position? And at how many visits?
- 3) Who should perform the OBPM (nurse/physician)?
- 4) How should the average OBPM value be determined?
- 5) Which device should be used for the OBPM?
- 6) How should the SBPM be performed? How often? How many days?
- 7) How should the average SBPM value be determined?
- 8) How should the ABPM be performed?
- 9) How should the average ABPM value be determined? Daytime, 24-h ABPM
- 10) Can we classify patients as masked hypertensive when they are among antihypertensive treatment?
- 11) Which thresholds do we hold on for ABPM, OBPM and SBPM? Should we revise the current definition of masked hypertension in order in order to take into account patients with all blood pressure values instead of only those with blood pressure values around the thresholds?

References

1. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002;40:795-6.
2. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;23:697-701.
3. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation* 2001;104:1385-92.
4. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999;131:564-72.
5. Sakaguchi K, Horimatsu T, Kishi M, Takeda A, Ohnishi Y, Koike T, Fujisawa T, Maeda M. Isolated home hypertension in the morning is associated with target organ damage in patients with type 2 diabetes. *J Atheroscler Thromb* 2005;12:225-31.
6. Bjorklund K, Lind L, Zethelius B, Andren B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation* 2003;107:1297-302.
7. Lurbe E, Torro I, Alvarez V, Nawrot T, Paya R, Redon J, Staessen JA. Prevalence, persistence, and clinical significance of masked hypertension in youth. *Hypertension* 2005;45:493-8.
8. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342-9.
9. Poncelet P, Clerson P, Ribstein J, Bassous M, Gres CS. Is masked hypertension an artefact due to the blood pressure measurement method and threshold effects? What is the true prevalence of masked hypertension? *J Hypertens* 2005;23:A1-2.
10. Matsuoka S, Awazu M. Masked hypertension in children and young adults. *Pediatr Nephrol* 2004;19:651-4.
11. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. In clinical practice, masked hypertension is as common as isolated clinic hypertension: predominance of younger men. *Am J Hypertens* 2005;18:589-93.
12. Stabouli S, Kotsis V, Tzoumanidis S, Papamichael C, Constantopoulos A, Zakopoulos N. White-coat and masked hypertension in children: association with target-organ damage. *Pediatr Nephrol* 2005;20:1151-5.
13. Obara T, Ohkubo T, Funahashi J, Kikuya M, Asayama K, Metoki H, Oikawa T, Hashimoto J, Totsune K, Imai Y. Isolated uncontrolled hypertension at home and in the office among treated hypertensive patients from the J-HOME study. *J Hypertens* 2005;23:1653-60.
14. Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? *Am J Hypertens* 2005;18:772-8.
15. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005;46:508-15.
16. Palatini P, Winnicki M, Santonastaso M, Mos L, Longo D, Zaetta V, Dal Follo M, Biasion T, Pessina AC. Prevalence and clinical significance of isolated ambulatory hypertension in young subjects screened for stage 1 hypertension. *Hypertension* 2004;44:170-4.
17. Belkic KL, Schnall PL, Landsbergis PA, Schwartz JE, Gerber LM, Baker D, Pickering TG. Hypertension at the workplace--an occult disease? The need for work site surveillance. *Adv Psychosom Med* 2001;22:116-38.

18. Selenta C, Hogan BE, Linden W. How often do office blood pressure measurements fail to identify true hypertension? An exploration of white-coat normotension. *Arch Fam Med* 2000;9:533-40.
19. Wing LM, Brown MA, Beilin LJ, Ryan P, Reid CM. 'Reverse white-coat hypertension' in older hypertensives. *J Hypertens* 2002;20:639-44.
20. La Batide-Alanore A, Chatellier G, Bobrie G, Fofol I, Plouin PF. Comparison of nurse- and physician-determined clinic blood pressure levels in patients referred to a hypertension clinic: implications for subsequent management. *J Hypertens* 2000;18:391-8.
21. Sala C, Santin E, Rescaldani M, Cuspidi C, Magrini F. What is the accuracy of clinic blood pressure measurement? *Am J Hypertens* 2005;18:244-8.
22. Mallion JM, Genes N, Vaur L, Clerson P, Vaisse B, Bobrie G, Chatellier G. Detection of masked hypertension by home blood pressure measurement: is the number of measurements an important issue? *Blood Press Monit* 2004;9:301-5.
23. Cuspidi C, Meani S, Fusi V, Valerio C, Catini E, Magrini F, Zanchetti A. Isolated ambulatory hypertension and changes in target organ damage in treated hypertensive patients. *J Hum Hypertens* 2005;19:471-7.
24. Bobrie G, Genes N, Vaur L, Clerson P, Vaisse B, Mallion JM, Chatellier G. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med* 2001;161:2205-11.
25. Rasmussen SL, Torp-Pedersen C, Borch-Johnsen K, Ibsen H. Normal values for ambulatory blood pressure and differences between casual blood pressure and ambulatory blood pressure: results from a Danish population survey. *J Hypertens* 1998;16:1415-24.
26. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens* 1995;13:1377-90.
27. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983;249:2792-8.
28. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999;282:539-46.
29. Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997;15:357-64.
30. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801.
31. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;348:2407-15.
32. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48.
33. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998;16:971-5.
34. Kannel WB. Role of blood pressure in cardiovascular morbidity and mortality. *Prog Cardiovasc Dis* 1974;17:5-24.
35. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-46.
36. Celis H, Fagard RH. White-coat hypertension: a clinical review. *Eur J Intern Med* 2004;15:348-57.

37. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
38. Mann SJ, James GD, Wang RS, Pickering TG. Elevation of ambulatory systolic blood pressure in hypertensive smokers. A case-control study. *JAMA* 1991;265:2226-8.
39. Narkiewicz K, Maraglino G, Biasion T, Rossi G, Sanzuol F, Palatini P. Interactive effect of cigarettes and coffee on daytime systolic blood pressure in patients with mild essential hypertension. HARVEST Study Group (Italy). *Hypertension Ambulatory Recording Venetia Study. J Hypertens* 1995;13:965-70.
40. Vriz O, Piccolo D, Cozzutti E, Milani L, Gelisio R, Pegoraro F, Garavelli G, D'Este D, Palatini P. The effects of alcohol consumption on ambulatory blood pressure and target organs in subjects with borderline to mild hypertension. HARVEST Study Group. *Am J Hypertens* 1998;11:230-4.
41. Palatini P, Graniero GR, Mormino P, Nicolosi L, Mos L, Visentin P, Pessina AC. Relation between physical training and ambulatory blood pressure in stage I hypertensive subjects. Results of the HARVEST Trial. *Hypertension and Ambulatory Recording Venetia Study. Circulation* 1994;90:2870-6.
42. Pickering TG, Gerin W. Ambulatory blood pressure and reactivity. *J Hypertens* 1992;10:299-300.
43. Bombelli M, Sega R, Facchetti R, Corrao G, Friz HP, Vertemati AM, Sanvito R, Banfi E, Carugo S, Primitz L, Mancia G. Prevalence and clinical significance of a greater ambulatory versus office blood pressure ('reversed white coat' condition) in a general population. *J Hypertens* 2005;23:513-20.
44. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
45. Eilertson E, Humerfelt S. The observer variation in the measurement of arterial blood pressure. *Acta Med Scand* 1968;184:145-57.
46. Vriz O, Soon G, Lu H, Weder AB, Canali C, Palatini P. Does orthostatic testing have any role in the evaluation of the young subject with mild hypertension?: an insight from the HARVEST study. *Am J Hypertens* 1997;10:546-51.
47. Narkiewicz K, Piccolo D, Borella P, Businaro R, Zonzin P, Palatini P. Response to orthostatic stress predicts office-daytime blood pressure difference, but not nocturnal blood pressure fall in mild essential hypertensives: results of the harvest trial. *Clin Exp Pharmacol Physiol* 1995;22:743-7.
48. Raikonen K, Matthews KA, Kondwani KA, Bunker CH, Melhem NM, Ukoli FA, Asogun A, Jacob RG. Does nondipping of blood pressure at night reflect a trait of blunted cardiovascular responses to daily activities? *Ann Behav Med* 2004;27:131-7.

Chapter 8

The white coat effect does not change with multiple measurement visits

Abstract

Objective

To investigate the prevalence of the white coat effect (WCE) and white coat hypertension (WCH) on multiple blood pressure measurement occasions in hypertensive patients with and without treatment. In addition, we investigated whether the WCE sustains on multiple OBPM visits.

Design

Patients performed office blood pressure measurements (OBPM) at eight visits (3 readings per visit) and self blood pressure measurements (SBPM) for one week prior to each visit (42 readings per week) in a period of 1 year. All measurements were performed with the same automatic device (Omron 705CP). Additionally, 24-h ambulatory blood pressure monitoring (ABPM) was performed at the start and at the end of the trial. At the start, patients were untreated and subsequently treatment was based on their SBPM values at each visit. WCH was defined as an OBPM value ≥ 140 and or 90 mmHg and a SBPM or daytime ABPM value $< 135/85$ mmHg, also for treated patients. In addition we determined the prevalence of a substantial WCE (OBPM 20 mmHg systolic or 10 mmHg diastolic higher than SBPM or daytime ABPM).

Setting

Patients were recruited at hospital or general practice.

Patients

A total 163 mild-to-moderate hypertensive patients with a mean age of 56 years (56% males).

Results

At eight blood pressure (BP) measurement occasions, 75% of all patients had once or more a substantial WCE and 57% had at least once WCH. The magnitude of the WCE was significantly related to the average OBPM and SBPM for treated but not for untreated patients. Within the range of the average BP values in the present study, the prevalence of patients with substantial WCE did not change. On three or more BP measurement occasions one-third of all patients consistently had substantial WCE and 14% consistently had WCH.

Conclusion

For some patients WCH or a substantial WCE sustains on multiple OBPM visits. Especially in untreated patients, the magnitude of the WCE highly fluctuates. Therefore, to prevent misdiagnosis, it deserves recommendation to perform SBPM and or ABPM in addition to OBPM.

Introduction

Conventional blood pressure (BP) measurement performed in the clinical environment can easily elicit a white coat effect (WCE), a transient rise in BP that dissipates when a patient leaves the environment¹. The WCE can lead to a situation that a patient has an elevated BP at the clinical measurement, whereas the BP is normotensive outside the physician's office: so-called white coat hypertension (WCH)². Thus, WCE is a measure of BP change whereas WCH is a measure of BP level. Detection of WCH and the extent of the WCE are highly relevant, otherwise it will lead to unnecessary drug prescription and to increased overall healthcare costs. WCE is not considered as a risk factor for stroke and other cardiovascular events, because the increase in BP is transient and may be idiosyncratic to the clinic setting^{1,3}. However, results from the Ohasama-study showed that WCH is not completely innocent as subjects with WCH had an approximately 2-fold higher risk of eventually developing hypertension as compared to sustained normotensives⁴.

In order to take appropriate measures for dealing with a WCE and/or WCH it is necessary to find answers to questions such as: 1) Does it disappear with repeated measurements? and 2) What influence has treatment and/or decreased BP level on the WCE and/or WCH?

Currently, there are two suitable methods for detecting the WCE and WCH: self blood pressure measurement (SBPM) and ambulatory blood pressure monitoring (ABPM)^{1,5,6}. In our study, we used both methods on repeated BP measurement occasions.

Methods

Patients participated in the HOMERUS-trial of which the design has been described in detail elsewhere⁷. In brief, 216 Patients, who performed SBPM, were recruited from the outpatient departments of four participating university hospitals and from general practices. Both previously treated and untreated patients with essential hypertension, with average BP values that ranged between 140/90 mmHg and 200/120 mmHg, qualified for inclusion. The duration of the trial was one year during which OBPM and SBPM was performed eight times. At entry into the study, any existing antihypertensive therapy was discontinued whenever possible and patients entered a placebo run-in period of four weeks duration, before study treatment was initiated. After each visit, medication was adjusted according to a stepwise treatment schedule based on the SBPM results. The target SBPM values were set at 140 mmHg systolic and 90 mmHg diastolic and the lower limit at 120 mmHg systolic and 80 mmHg diastolic. Treatment decisions were taken at the coordinating

centre so that both the doctor and patient were blinded for their medication. Laboratory assessments and 24-h ambulatory blood pressure monitoring (ABPM) as a reference standard were performed at the end of the run-in period and at the end of the trial. All patients gave their informed consent and the study was approved by the ethics committees of all participating centres before inclusion of patients into the study.

Blood pressure measurements

At every visit, three consecutive OBPMs were performed in the hospital or at the general practitioners clinic. SBPM was performed six times a day (three in the morning and three in the evening) for a 7-day period, prior to every visit. Patients were requested to register their self-measurements on a form and to print out each measurement. The SBPM value was determined from the average of 42 measurements. Both OBPM and SBPM were always performed at the non-dominant arm in sitting position after at least 5 min of rest, using the same fully automated validated device (Omron HEM-705 CP)⁸. ABPM was performed with a Spacelabs automatic device. Measurements were taken every 15 min between 07.00 and 23.00h and every 30 min at night. The average daytime ABPM value was calculated from 09.00 to 21.00h on the first day without the initial hour. Average nocturnal ABPM was determined from 0.100 to 0.600h.

Laboratory analyses

Blood was drawn from fasting patients for determination of blood glucose, serum cholesterol (total and HDL-cholesterol) and serum creatinine. Urinary (micro-) albumin concentrations were assessed from two consecutive 24-h urine collections. All micro-albumin measurements were performed in the same laboratory.

White coat hypertension/White coat effect

At each visit the number of patients with WCH and a WCE was determined with SBPM, (self-WCH and self-WCE) and daytime ABPM (ambulatory-WCH and ambulatory-WCE). WCH was defined according to the ESH guideline⁹: an OBPM value equal to or higher than 140 mmHg systolic and/or 90 mmHg diastolic with SBPM or a daytime ABPM lower than 135 mmHg systolic and 85 mmHg diastolic.

An OBPM value that was at least 20 mmHg systolic or 10 mmHg diastolic higher than the corresponding SBPM or daytime ABPM value was regarded as clinically relevant, so-called substantial WCE¹⁰. For this reason the prevalence of patients with a WCE was determined as the number of patients with a

substantial WCE. The WCE values were defined as the differences between the daytime ABPM or SBPM values and OBPM values.

Differences within groups were analysed with the Student t-test. The relationship between WCE values and ABPM or SBPM were determined with the Bland-Altman approach. Correlation was determined using linear regression. A p -value <0.05 was considered significant (2-sided).

Results

From the 216 patients 19 patients did not complete the study because they withdrew consent ($n=18$) or had an adverse event ($n=1$). Another 34 patients were not included in the analysis because they missed either one follow-up visit or skipped one SBPM session prior to a visit ($n=24$) or their previous treatment could not be stopped ($n=10$). These 53 patients did not differ from the 163 patients whose characteristics are illustrated at Table 8.1.

Table 8.1 Distribution of clinical characteristics at inclusion.

Parameter	($n=163$)
Males, n (%)	91 (55.8)
Age, yr (SD)	55.7(10.0)
BMI, kg/m ² (SD)	27.7 (4.4)
Smoking, n (%)	30 (18.4)
Alcohol, n (%)	126 (77.3)
Glucose, mmol/l (SD)	5.4 (0.9)
Cholesterol, mmol/l (SD)	5.7 (1.0)
Creatinine, μ mol/l (SD)	82.5 (14.5)
Microalbuminuria, mg/24-h ^a	10.0
Number of patients on previous antihypertensives, n (%)	
0, n (%)	49 (30.1)
1, n (%)	66 (40.5)
2, n (%)	36 (22.1)
3 or more, n (%)	12 (7.3)

BMI indicates body mass index; ^a results are given as median.

BP and heart rate values for all eight visits throughout the trial are illustrated in Table 8.2. Average BP decreased with every visit and at all visits SBPM values were lower than corresponding OBPM values just as the heart rate that was lower when self-measured at home than when measured in the physician's office. The heart rate did not decrease with lower BP values. Differences between daytime ABPM and SBPM were largely decreased at the end of the trial.

Table 8.2 Blood pressure and heart rate values (mean $\pm$ SD) at eight visits of the trial.

	OBPM			SBPM			ABPM daytime		
	mean (SD)			mean (SD)			mean (SD)		
	SBP (mmHg)	DBP (mmHg)	HR (beats/min)	SBP (mmHg)	DBP (mmHg)	HR (beats/min)	SBP (mmHg)	DBP (mmHg)	HR (beats/min)
Months									
0	165 (19)	96 (9)	77 (12)	155 (18)	92 (9)	71 (8)	148 (15)	92 (10)	78 (9)
1	155 (21)	92 (11)	78 (11)	145 (18)	86 (9)	70 (8)			
2	153 (21)	91 (10)	75 (11)	142 (16)	85 (9)	70 (8)			
4	149 (19)	88 (10)	76 (11)	137 (13)	82 (8)	70 (9)			
6	144 (16)	85 (9)	75 (12)	136 (10)	81 (6)	69 (9)			
8	144 (16)	85 (9)	76 (13)	135 (10)	81 (7)	69 (9)			
10	143 (17)	84 (9)	76 (12)	134 (10)	80 (6)	69 (10)			
12	143 (17)	84 (9)	75 (12)	133 (9)	80 (6)	69 (9)	131 (11)	81 (9)	76 (11)

OBPM indicates office blood pressure measurement; SBPM, self blood pressure measurement; ABPM, ambulatory blood pressure measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Figure 8.1 shows that the number of patients with WCH significantly increased with decreasing BP values ($r=0.9$; $p<0.05$). At the start of the trial when patients were untreated and had a mean BP value of 165/96 mmHg, the WCH prevalence was 9%. At the end of the trial when patients were treated and had a BP value of 143/84 mmHg on average, the WCH prevalence was 22%. The prevalence of subjects with substantial WCE remained rather similar (31%) throughout the trial ($r=-0.7$; ns)

When patients had WCH at one visit there was a chance of 44% that they had also WCH at the next visit as found with SBPM. For substantial WCE, the mean overlap was 57%.

Figure 8.1 Prevalence of patients with white coat hypertension according to the ESH definition as determined with self blood pressure measurement (SBPM) (○; $r=0.9$ ($p<0.05$; straight line)) and ABPM (●; dashed line). In addition, the prevalence of patients with a substantial white coat effect as determined with SBPM (□; $r=-0.7$ (ns; straight line)) and ambulatory blood pressure measurement (ABPM) (■; dashed line).

Figure 8.2 shows that more than half the patients were at least once classified as having WCH and 12% on four or more occasions. At eight BP measurement occasions, 75% of all patients had at least once a substantial WCE and one-third of all patients had substantial WCE on four or more occasions from eight.

Figure 8.2 Indicates, for each visit, the prevalence of patients with white coat hypertension ($\square$) and of patients with a substantial white coat effect ($\blacksquare$) as determined with office and self blood pressure measurement.

Figure 8.3 illustrates the consistency of substantial WCE and WCH and shows that a quarter of all patients had WCH on at least two subsequent measurement occasions and 14% had WCH on three or more subsequent occasions. For substantial WCE this prevalence was higher: 45% had substantial WCE twice or more times in a row and 28% three times or more.

Figure 8.3 Indicates, the consistency of white coat hypertension ($\square$) and of a substantial white coat effect ($\blacksquare$) on two or more blood pressure measurement occasions in a row, as determined with office and self blood pressure measurement

Results indicated that, for untreated patients, the systolic WCE values, as determined with ABPM had a significant relationship ($p<0.001$) with the average OBPM and ABPM values (Figure 8.4a). However, this was not the case when the WCE value was determined with SBPM. When patients were treated there were positive significant relationships between the average OBPM and SBPM values and the white coat effect values. When determined with ABPM only the systolic white coat effect values was positive significantly related with the average OBPM and ABPM (Figure 8.4b).

Figure 8.4a Left: Bland-Altman plots for the differences between office blood pressure measurement (OBPM) and self blood pressure measurement (SBPM) as a function of the average of OBPM and SBPM in untreated patients. Right: the differences between office blood pressure measurement (OBPM) and ambulatory blood pressure measurement (ABPM) as a function of the average of OBPM and ABPM in untreated patients. The line indicates that the relationship was statistically significant ($p<0.001$). Studies were weighted for the number of subjects.

Figure 8.4b Left: Bland-Altman plots for the differences between office blood pressure measurement (OBPM) and self blood pressure measurement (SBPM) as a function of the average of OBPM and SBPM in treated patients. Right: the differences between office blood pressure measurement (OBPM) and ambulatory blood pressure measurement (ABPM) as a function of the average of OBPM and ABPM in treated patients. The lines indicate that the relationship was statistically significant ($p < 0.001$). Studies were weighted for the number of subjects.

Discussion

In the present study, three-quarters of the population had a substantial WCE in at least one out of eight BP measurement occasions. At each visit, one-third of all subjects had a substantial WCE. One-third of all patients consistently had a substantial WCE and 14% consistently had WCH, on three or more BP measurement occasions. The prevalence of WCH increased significantly as BP decreased but the prevalence of patients with a substantial WCE remained similar throughout the study. The height of the WCE was significantly related to the average OBPM and SBPM value when patients were treated but not when patients were untreated. When patients had a substantial WCE or WCH at one visit the probability of a similar diagnosis at the next visit was about 57% and 44% respectively.

The present study should be interpreted within the context of its limitations. All subjects were untreated at the first visit and then were provided antihypertensive treatment, based on their SBPM values, from the second visit

onward. For this reason it may seem useless to determine the prevalence of subjects with WCH after the first visit as formally treated subject cannot be classified as so. However, we are of the opinion that it is clinically relevant to determine this prevalence as it has serious consequences for a patient's treatment and overall healthcare costs. When patients would be treated based on their OBPM values WCH would lead to additional treatment, which is in fact unnecessary. In the present study, all patients were treated according to their SBPM results and thus most patients with WCH did not receive additional treatment. This may have increased the chance of consistently finding WCH or a WCE at the next visit. On the other hand, results indicated that the number of patients with a substantial WCE did not change with changing BP values and/or changing treatment, within the range of the obtained BP values. Commonly, ABPM was performed one week earlier than the corresponding OBPM. This may have had a minor influence on the WCE results as determined with OBPM and ABPM. Additionally, patients were mild to moderate hypertensives and therefore these results cannot be extrapolated to a regular population.

Several studies have investigated the topics of WCH prevalence with results that varied from 15% to over 50% in patients with mildly elevated OBPM values¹¹ and around 10%^{12,13} in the population at large and in clinical practice. In contrast to WCH, most studies to the WCE involved the height of its value instead of prevalence. Pickering *et al.* investigated whether there is a difference in WCE between treated and untreated patients and found a reduction in WCE values during treatment¹. Recently, Stergiou *et al.* showed in a study among 276 treated and untreated patients that there was a trend towards a lower WCE in treated patients¹⁴. Stenehjem *et al.* have reported that the ambulatory-WCE among 75 untreated hypertensives largely attenuated during repeated measurements¹⁵.

The few studies that researched the prevalence of WCE found a similar prevalence for treated and untreated patients within the studies but a different WCE prevalence between the studies. Myers, who sampled data from studies for the WCE prevalence reported that 70% of the patients had a WCE¹⁰. Stergiou *et al.* found a self-WCE prevalence of 28% and 21% and an ambulatory-WCE of 27% and 20% in 138 untreated and 138 treated patients respectively¹⁴.

The above mentioned studies on the prevalence of WCE used the same definition as was used in this paper for substantial WCE: the difference between OBPM and daytime ABPM or the difference between OBPM and SBPM of 20 mmHg systolic or 10 mmHg diastolic. Initially, these values were based on differences between OBPM and 24-h ABPM, but were taken over by other studies that used the same criteria for SBPM and daytime ABPM¹⁴. The clinical importance of these values¹⁰ was underlined by Lewington *et al.*¹⁶ who

showed that each difference of 20 mmHg systolic BP or, approximately equivalently, 10 mmHg casual diastolic BP is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischemic heart disease and from other vascular causes.

In most studies about the prevalence of the WCE and/or WCH the SBPM and OBPM values were obtained with different devices and the OBPM was performed with a mercury sphygmomanometer which is highly subject to observer bias¹⁷ and may therefore have led to a larger WCE. In the present study however, we used the same validated oscillometric device for OBPM and SBPM. This means that there were no differences because of the device and therefore the prevalence of patients with a WCE, as determined with SBPM, might be underestimated as compared to other studies. Studies that determined the WCE by both ABPM and SBPM had different results. Den Hond *et al.* found a larger WCE on SBPM than with ABPM in 239 patients⁶. In the study of Stergiou *et al.* the ambulatory and self-measurement provided similar WCE results. Despite the lack of difference in the mean WCE value they concluded that SBPM is not as appropriate as ABPM in the detection of WCE but is useful as a screening test⁵. However, one should be cautious to conclude that ABPM is superior to SBPM, as ABPM is also liable to a pressor effect, the so-called ABPM-effect. Hermida *et al.* and Calvo *et al.* found a significant increase in BP during the first hours of ABPM^{18,19} and there are indications, at least in adolescents, that this effect wanes when patients have a repeated ABPM²⁰. Therefore, at the second measurement, a decreased daytime ABPM value may be partly ascribed to a lower ABPM-effect besides the effect of drug treatment.

In contrast to former studies to WCH and the WCE, The present study provides us with data from multiple measurements of OBPM, SBPM and ABPM in treated and untreated antihypertensive subjects. The clinical relevance of the analysis lies in the fact that it reveals whether it is useful or not to provide multiple OBPM visits before institution of antihypertensive treatment. In addition it shows the influence of antihypertensive treatment and/or changing BP values on the magnitude and prevalence of the WCE and the prevalence of WCH among hypertensive patients. From a clinical aspect it would be interesting whether some antihypertensive drugs are more liable to WCE than others. However, as all subjects in our study were treated according to a stepwise treatment schedule and thus there was little variation among treatment we could not investigate this subject.

According to ESH recommendations a number of measurements should be made on different occasions over a number of weeks or months before diagnostic or management decisions are made as the WCE may persist after several visits². However when three OBPM visits should be performed there would be still almost one-third of all patients with substantial WCE at three or

more subsequent visits and with WCH this was 14%. In addition, the chance of finding WCH three times in a row strongly increases when patients have BP values around the upper limits of the ESH definition. Consequently, frequent visits at which OBPM is determined, would still lead to wrong diagnosis and treatment. This may cause inconvenience for the patient as many of the side effects of therapy, including dizziness, vertigo, lethargy, fatigue, peripheral coldness, probably is related to BP values that are too low²¹. Therefore, to prevent this misdiagnosis it deserves recommendation to perform SBPM in addition to OBPM. The height of the WCE value was significantly related to the average SBPM and OBPM value when patients were treated but not when patients were untreated. The reason for this probably lies in the high BP variability as is frequently seen in untreated hypertensive patients. This indicates that the height of the WCE is more predictable when patients are treated than when untreated.

In conclusion, on eight measurement occasions three-quarters of all hypertensive patients are liable to a substantial WCE and 60% to WCH. The prevalence of substantial WCE does not change with decreasing BP values within the range of the average BP values in the present study. In untreated patients the WCE value is not related to the average OBPM and SBPM value. The number of patients with WCH increases when patients have BP values close to the upper limits of the WCH definition. Finally, performing frequent OBPMs at several occasions is not sufficient to exclude a substantial WCE and WCH in all patients. Consequently, this may lead to unnecessary drug prescription. Therefore, it deserves recommendation to perform SBPM or ABPM in addition to OBPM.

References

1. Pickering TG, Gerin W, Schwartz AR. What is the white-coat effect and how should it be measured? *Blood Press Monit* 2002;7:293-300.
2. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancina G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48.
3. Millar JA, Isles CG, Lever AF. Blood pressure, 'white-coat' pressor responses and cardiovascular risk in placebo-group patients of the MRC Mild Hypertension trial. *J Hypertens* 1995;13:175-83.
4. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Arch Intern Med* 2005;165:1541-6.
5. Stergiou GS, Zourbaki AS, Skeva, II, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *Am J Hypertens* 1998;11:820-7.
6. Hond ED, Celis H, Fagard R, Keary L, Leeman M, O'Brien E, Vandenhoven G, Staessen JA. Self-measured versus ambulatory blood pressure in the diagnosis of hypertension. *J Hypertens* 2003;21:717-22.
7. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
8. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. PG -. *Blood Press Monit* 1996 Feb;1:55-61. 1996:55-61.
9. O'Brien E, Asmar R, Beilin L, Imai Y, Mancina G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;23:697-701.
10. Myers MG. The white-coat effect in treated hypertension. *Blood Press Monit* 1996;1:247-249.
11. Celis H, Fagard RH. White-coat hypertension: a clinical review. *Eur J Intern Med* 2004;15:348-57.
12. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. In clinical practice, masked hypertension is as common as isolated clinic hypertension: predominance of younger men. *Am J Hypertens* 2005;18:589-93.
13. Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R, Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancina G. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation* 2001;104:1385-92.
14. Stergiou GS, Efsthathiou SP, Argyraki CK, Roussias LG, Mountokalakis TD. White coat effect in treated versus untreated hypertensive individuals: a case-control study using ambulatory and home blood pressure monitoring. *Am J Hypertens* 2004;17:124-8.
15. Stenehjem AE, Os I. Reproducibility of blood pressure variability, white-coat effect and dipping pattern in untreated, uncomplicated and newly diagnosed essential hypertension. *Blood Press* 2004;13:214-24.
16. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.

17. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
18. Hermida RC, Calvo C, Ayala DE, Fernandez JR, Ruilope LM, Lopez JE. Evaluation of the extent and duration of the "ABPM effect" in hypertensive patients. *J Am Coll Cardiol* 2002;40:710-7.
19. Calvo C, Hermida RC, Ayala DE, Lopez JE, Fernandez JR, Dominguez MJ, Mojon A, Covelo M. The 'ABPM effect' gradually decreases but does not disappear in successive sessions of ambulatory monitoring. *J Hypertens* 2003;21:2265-73.
20. Rucki S, Feber J. Repeated ambulatory blood pressure monitoring in adolescents with mild hypertension. *Pediatr Nephrol* 2001;16:911-5.
21. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.

Chapter 9

Home blood pressure measurement,
a systematic review

WJ Verberk, AA Kroon, AGH Kessels, PW de Leeuw

J Am Coll Cardiol. 2005;46:743-51.

Abstract

Aim

To review the literature on home blood pressure measurement (HBPM) and to provide recommendations regarding HBPM assessment.

Background

Although many papers on HBPM have been published, there has been no systematic analysis of the literature on how data obtained with HBPM should be interpreted.

Methods

Observational studies on HBPM, published after 1992, as identified by PUBMED, EMBASE and Cochrane literature searches. Studies were selected if they met the following criteria: 1) self-measurements had been performed with validated devices, 2) measurement procedures were described in sufficient detail and 3) papers clearly explained how final HBPM results were calculated upon which conclusions and/or treatment decisions were based.

Results

Office blood pressure measurement (OBPM) yields higher blood pressure values than HBPM. For systolic blood pressure, differences between OBPM and HBPM increase with age and the height of office pressure. Differences also tend to be greater in males than in females and greater in patients without than in those with antihypertensive treatment. Furthermore, HBPM can diagnose normotension with almost absolute certainty, it correlates better with target organ damage and cardiovascular mortality than OBPM, it enables prediction of sustained hypertension in patients with borderline hypertension and proves to be an appropriate tool for assessing drug efficacy.

Conclusion

Despite some limitations and although more data are needed, HBPM is suitable for routine clinical practice.

Introduction

Home blood pressure measurement (HBPM) has become increasingly popular and is now gaining more and more acceptance by patients and clinicians. Several factors can account for this phenomenon. First of all, reliable automatic devices for HBPM have become available, and their performance characteristics can easily be retrieved via the internet¹. Secondly, HBPM is less liable to observer bias and the white coat effect than office blood pressure measurements (OBPM)². In addition, with HBPM more measurements can be obtained within a limited period of time. Finally, HBPM data correlate better with daytime values of ambulatory blood pressure measurement (ABPM)³. However, the introduction of HBPM into clinical practice has also faced us with new problems. These include questions as: how many measurements are needed to estimate a patient's usual blood pressure (BP), what are normal values for HBPM, how does antihypertensive treatment affect HBPM, and to what extent can HBPM predict prognosis? The intention of this review, therefore, is to evaluate current knowledge about HBPM to find answers to these questions. To this end, we performed a systematic review of the literature on HBPM.

Methods

Identification of papers

We performed systematic searches of HBPM in PUBMED, EMBASE and the Cochrane database. The search strategy used six key words in various combinations: BP, hypertension, self-measurement, home measurement, ambulatory measurement, and compliance. Additional studies were found from reference lists of identified articles and reviews.

Study selection

Because the first protocol with guidelines for validation of BP monitoring devices dates back from July 1990⁴, we wanted to include in our review only those papers that have been published after that time. Allowing for some lag time before the guidelines were fully implemented, we took 1992 as the starting year for our literature search. Decisions on inclusion of studies into the systematic review were based on three criteria:

- 1) Self-measurements were performed with devices that have passed the validation protocols of the British Hypertension Society (BHS)⁴, Association

for the Advancement of Medical Instrumentation (AAMI)⁵ and/or European Society of Hypertension (ESH)⁶;

- 2) HBPM or self-measurement procedures used were described in sufficient detail;
- 3) The methods section clearly explained how authors calculated from their original data the finally reported home blood pressure (HBP) results.

Two investigators screened the full text of all potentially relevant articles. When more than one paper by the same author or research group was available, these were included for analysis only when it was likely that a different sample had been used.

Data extraction

Papers that fulfilled the selection criteria and provided both OBPM and HBPM data were collected. When multiple drug treatment studies were performed using the same population, only the results of the first study mentioned were used for analysis. Studies that combined subjects with and without antihypertensive drug treatment, without the possibility to distinguish both groups, were excluded for analysis.

Data synthesis

To test for differences between OBPM and HBPM, we pooled the results weighted with inverse variances (direct pooling)⁷. In case the variance was not reported, we imputed the highest variance of the study that was included. Changes in home and office BP, obtained before and after treatment, were compared conservatively by considering these outcomes as unpaired data. To investigate whether age and gender could explain heterogeneity in differences between OBPM and HBPM, we performed linear regression analysis with age and gender (as proportion of men) as independent variables and the difference between OBPM and HBPM as the dependent variable. All statistical calculations were performed using SPSS (SPSS Inc., Chicago, Illinois).

Results

How many measurements are needed?

To determine the number of measurements that are needed to obtain a reliable estimate of a patient's usual blood pressure when applying HBPM, several studies assessed the reproducibility and/or accuracy of the technique⁸⁻¹¹. The results from these studies are summarised in Table 9.1. From all studies, which addressed the number of measurements required to obtain an accurate

impression of BP for a period of at least one month⁸⁻¹¹, we may conclude that the minimum number of measurements should be two duplicates a day (twice in the morning and twice in the evening) for three consecutive days with exclusion of BP readings taken at the first day.

Table 9.1 Studies on Accuracy and Reproducibility of Home Blood Pressure Measurement.

Ref	n	Population	Device	Frequency of measurements		Mathematical method	Proposed number of measurements
				Consecutive readings	Days Time of measurement		
8	74	Elderly Hypertensives	MS	1	10 M, lying in bed, M, after 10 min standing, E, standing before going to bed, E, lying in bed for 10 min	T-test, Variability (SD)	1 reading/day for 3 consecutive days
9	189	Hypertensives	AOD	2	3 M, 0630-1000 h, work days E, 1700-2300 h	Test-re-test, Variability (SD), Correlation with ABPM	Average of 2 nd and 3 rd working day
10	48	Hypertensives	SOD	1	8 M E At Work	Test-re-test, Variability (SD), G-theory	1 reading at work and 1 consecutive days for reliable estimates for 2 months.
11	871	Normotensives & Hypertensives	SOD	1	28 M, <1h after awakening	Variability (SD)	1 reading/day in the morning for 3 consecutive days

ABPM, ambulatory blood pressure measurement; AOD, automatic oscillometric device; E, evening; M, morning; MS, mercury sphygmomanometer; SOD, semi-automatic oscillometric device.

Upper limit of normal values

Table 9.2 provides an overview of studies that have addressed the issue of normal values. Various methods were used to obtain normal values¹²⁻¹⁸, namely:

- 1) Calculating the mean + two standard deviations for HBPM data in a population and to consider this as the upper limit of normal (normal distribution criterion)¹⁴;
- 2) Computing the 95th percentile of the distribution of HBPM data in subjects who were normotensive on conventional sphygmomanometry and to consider every value above that percentile as abnormal (percentile criterion)¹³⁻¹⁵;
- 3) Determining the self-recorded BP that corresponds to a conventional (office) BP of 140/90 mmHg [correspondence^{12-14,16-18} or regression criterion^{13,14,18}].

- 4) Conducting a long-term follow-up trial in which normal values are based on the morbidity and mortality patterns from hypertension-related complications¹⁶.

Taken together, the data from these studies suggest that the upper limit for normal HBPM values should be set at 135 mmHg systolic and 85 mmHg diastolic.

Table 9.2 Studies Investigating the Upper Limit of Normal Values.

Ref n	Age (yrs)	Mathematical method ^a	Proposed normal values (mmHg)
12 390	20-59	Correspondence criterion ^a	128/84
13 562	51	1) 95 th percentile (476 normotensive subjects)	1) 140/83
		2) Correspondence criterion ^a	2) 140/86
		3) Regression criterion ^b	3) 137/83
14 5422 (meta-analysis)	^c	1) Mean + 2SDs	1) 137/89
		2) 95 th percentile	2) 135/86
		3) Correspondence criterion ^a	3) 129/84
		4) Regression criterion ^b	4) 125/79
15 2401 (International database)	41	95 th percentile	137/85
16 1913	61	10% increase in mortality risk taken from the lowest point of mortality risk obtained during a 5 year follow-up study	137/84 66 en 83)
17 503	47	Correspondence criterion ^a	133/86
18 1438	46	1) Regression criterion ^b	1) 130/81
		2) Correspondence criterion ^a	2) 132/83

^a Calculation of the home blood pressure measurement (HBPM) value at the same percentile as that corresponding to an office blood pressure measurement (OBPM) of 140/90 mmHg; ^b calculation of the HBPM value corresponding to an OBPM value of 140/90 mmHg using the regression line between HBPM and OBPM; ^c not specified. SD: standard deviation

Differences between HBPM and OBPM

A pooled analysis of untreated subjects in the studies^{13,17,19-32} is listed in Table 9.3 and shows that the mean overall difference between OBPM and HBPM was 6.9 mmHg (95% confidence interval [CI] 6.6 to 7.2, $p<0.001$) for systolic BP (SBP), and 4.9 mmHg (95% CI 4.7 to 5.1, $p<0.001$) for diastolic BP (DBP). Differences between OBPM and HBPM increase with age for SBP but not for DBP (Figure 9.1). Bland-Altman analysis of the data shows that the difference between OBPM and HBPM also increases significantly with higher SBP (Figure 9.2) but not DBP. Finally, a higher percentage of males in a study population resulted in larger differences between OBPM and HBPM for SBP ($p<0.01$).

Table 9.3 Comparison Between OBPM and HBPM: Schematic Overview of Studies Among Untreated Subjects.

Ref	Population	n	Age (yrs)	Men (%)	Frequency of HBPM		Frequency of OBPM		HBPM (mmHg)	OBPM (mmHg)
					Consecutive readings	Days	Consecutive readings	Days		
13	HT+NT	562	51	47	2	3	3	2	120/73	119/74
17	NT+HT	503	47	53	1	14	1	2	123/78	130/82 ^c
19	HT	46	51	59	3	21	?	2	134/86	157/97
20	NT	35	54	57	1	7	3	2	124/74 ^a	121/79
21	HT	1395	59	43	2	1	2	2	159/93 ^a	166/98
22	HT	247	50	46	3	7	3	2	143/92	155/100
23	HT	233	46	58	2	7	2	4	139/93	145/95 ^d
24	HT	760	55	50	1	8	3	1	155/95	162/99
25	NT+HT	1438	46	!!	3	2	3	2	119/75	128/82
26	HT	19	53	60	1	14	1	2	151/98	158/103
27	HT	25	59	60	1	10	1	2	143/84	169/95
28	NT	596	31	52	1	7	3	1	114/71 ^b	112/74 ^b
28	HT	38	31	52	1	7	3	1	129/82 ^b	132/94 ^b
29	HT	199	56	56	3	1	3	1	144/90	160/100
30	HT	33	47	48	2	5	3	2	145/93	144/96
31	HT	24	56	63	3	7	3	1	146/94	163/101
31	HT	10	53	50	3	7	3	1	143/92	157/100
32	HT	816	56	55	3	7	3	1	153/94	166/101

Office blood pressure measurement (OBPM) was assessed with a mercury sphygmomanometer by a physician and home blood pressure measurement (HBPM) was performed in the morning and in the evening with an automatic or semiautomatic device, unless mentioned otherwise; HBPM and OBPM results are presented as average values. ^a HBPM performed in the morning, evening and in the afternoon; ^b measurements performed with an aneroid sphygmomanometer; ^c OBPM performed with a semi-automatic device; ^d OBPM performed by a nurse; !!, not specified. HT, hypertensives; NT, normotensives.

Figure 9.1 Differences between systolic (left panel) and diastolic (right panel) office blood pressure measurement (OBPM) and home blood pressure measurement (HBPM) as a function of age in patients without antihypertensive treatment. Results were derived from 18 studies with a total of 6979 subjects (Table 9.3). The relationship was statistically significant for systolic pressure only ($P=0.036$). The regression line was calculated for equal proportions of males and females and studies were weighted for the number of subjects.

Studies among treated subjects^{20,21,24,26,28-35} are summarised in Table 9.4 and show a mean overall difference between OBPM and HBPM of 5.3 mmHg (95%

CI 5.1 to 5.6, $p<0.0001$) for SBP, and 3.1 mmHg (95% CI 2.9 to 3.3, $p<0.0001$) for DBP. In this group no relationship of these differences with age, gender distribution, or the height of DBP emerged. Although differences tended to be greater with higher pressures for SBP (Figure 9.2), the relationship failed to reach statistical significance. The OBPM-HBPM difference was significantly smaller in treated than in untreated patients.

Figure 9.2 Bland-Altman plots for the differences between systolic office blood pressure measurement (OBPM) and home blood pressure measurement (HBPM) as a function of the average of OBPM and HBPM in patients without (left panel) or with (right panel) antihypertensive treatment. Results were derived from the studies mentioned in tables 9.3 and 9.4. The relationship was statistically significant for untreated subjects only ($p=0.007$). Studies were weighted for the number of subjects.

Table 9.4 Comparison Between OBPM and HBPM: Schematic Overview of Studies Among Treated Hypertensive Subjects

Ref	N	Age (yrs)	Men (%)	Frequency of HBPM		Frequency of OBPM		HBPM (mmHg)	OBPM (mmHg)
				Consecutive readings	Days	Consecutive readings	Days		
20	72	56	60	1	7	3	2	134/81 ^b	158/97
21	1395	59	43	2	1	2	2	142/82 ^b	146/85
24	760	55	50	1	8	3	1	144/87	142/86
26	19	53	60	1	14	1	2	140/91	145/95
28	38	34	52	1	7	3	1	126/82	135/95 ^a
29	199	56	56	3	1	3	1	135/85	143/86
30	33	47	48	2	5	3	2	129/83	129/85
31	24	56	63	3	7	3	1	135/88	153/94
31	10	53	50	3	7	3	1	143/91	150/92
32	816	56	55	3	7	3	1	139/85	145/86
33	209	57	53	1	7 ^c	2	12	137/84	147/87
34	142	58	53	1	2 ^d	3	1	136/80	140/82
35	5211	70	49	3	4	3	2	146/82	152/85

Office blood pressure measurement (OBPM) was assessed with a mercury sphygmomanometer by a physician. Unless indicated otherwise, home blood pressure measurement (HBPM) was performed in the morning and in the evening with an automatic or semiautomatic device. HBPM and OBPM results are presented as average values. ^a Measurements performed with an aneroid sphygmomanometer; ^b measurements performed in the morning, evening and afternoon; ^c seven days per month for a period of one year; ^d HBPM performed in the morning, evening and at work.

HBPM in relation to antihypertensive drug treatment

Table 9.5 presents the studies that investigated drug efficacy by using both OBPM and HBPM^{21,24,26,29-32}. After pooled analysis, differences in OBPM appeared to be 20.1 mmHg (95% CI 19.6 to 20.7) and 13.6 mmHg (95% CI 13.3 to 14.0) for SBP and DBP, respectively, while for HBPM differences were 13.9 mmHg (CI 13.4 to 14.4) and 9.1 mmHg (CI 8.8 to 9.4), respectively. The falls in pressure after treatment were significantly larger for OBPM than for HBPM ($p < 0.0001$ for SBP and DBP).

Table 9.5 Assessment of Drug Efficacy by HBPM and OBPM

Ref	n	Age (y)	Men (%)	Frequency of HBPM		Frequency of OBPM		Untreated - Treated	
				Consecutive Readings	Days	Consecutive Readings	Days	Δ HBPM (mmHg)	Δ OBPM (mmHg)
21	1395	59	43	2	1	2	2	17/11 ^a	20/13
24	760	55	50	1	8	3	1	11/8	20/13
26	19	53	60	1	14	1	2	12/7	13/8
29	199	56	56	3	1	3	1	10/5	17/13
30	33	47	48	2	5	3	2	16/10	15/11
31	24	56	63	3	7	3	1	11/6	10/7
31	10	53	50	3	7	3	1	0/1 ^b	7/8 ^b
32	816	56	55	3	7	3	1	14/9	22/15

Office blood pressure measurement (OBPM) was assessed with a mercury sphygmomanometer by a physician. Home blood pressure measurement (HBPM) was assessed in the morning and in the evening with an automatic or semiautomatic device, unless indicated otherwise. ^a HBPM performed in the morning, evening and in the afternoon; ^b patients obtained placebo instead of regular treatment.

HBPM and cardiovascular outcome

Several trials have addressed the relationship between home measurements and target organ damage (TOD) and found that HBPM correlated better with TOD, in particular left ventricular hypertrophy than OBPM^{33,36}. It correlated as well with left ventricular mass index as ABPM did³⁷. Moreover, HBPM appears to be a better prognostic indicator with respect to cardiovascular mortality^{38,39} and cardiovascular events³⁹ than OBPM.

Discussion

How many measurements are needed?

Recently, results from the Ohasama study⁴⁰ indicated that one should obtain as many measurements as possible, although with any number of measurements HBPM was already superior to OBPM in predicting future risk.

Because it is possible that BP at home differs from BP at work due to job stress or other factors, BP recorded at work might, in such situations, give a better indication of the overall BP value¹⁰. Despite some discrepancies in the results with regard to morning and evening HBPM, the fact remains that the early morning surge has immense prognostic potential⁴¹⁻⁴⁴. For that reason, HBPM in the morning is probably more valuable as compared to evening HBPM in terms of assessing cardiovascular prognosis. On the other hand, Brook⁴⁵ showed that the accuracy of HBPM does not depend on a particular monitoring schedule parameter such as number of measurements per day, replications per measurement session, or total duration of home monitoring.

Taking all available information together, it seems that the minimum number of measurements should be two duplicates a day (twice in the morning and twice in the evening) for three consecutive days. Measurements on the first day are persistently higher than subsequent measurements, and for that reason the data from the first day should be discarded⁹.

Upper limit of normal values

Normal values for HBPM have been established on the basis of an international database composed by Thijs *et al.*¹⁵. Because the 95th percentile method for normotensive subjects was used for obtaining normal values, these normal data were not directly dependent upon OBPM values. In our view, the proclamation of HBPM normal data according to OBPM values, as has been done in other studies, is not a priori justified since OBPM values are highly variable and subject to observer bias as well as the white coat effect.

Preferably, normal values should be based on prognostic studies such as those from Tsuji *et al.*¹⁶, who defined hypertension as a BP value $\geq 137/84$ mmHg and normal BP as SBP < 137 mmHg and DBP between 66 en 83 mmHg. Fortunately, these values are in line with the reference values from the international database (namely 137/85 mmHg). In accordance with recent guidelines^{46,47}, it is fair to set the upper limit of normal values at 135 mmHg systolic and 85 mmHg diastolic.

Differences between OBPM and HBPM

Our analysis shows that the difference in SBP between OBPM and HBPM in untreated patients tends to be larger in men than in women and to rise with age and the level of BP. However, whether age and the degree of hypertension are independent predictors of the difference between OBPM and HBPM cannot be derived from the available data. We further found that the difference between OBPM and HBPM is greater before than during antihypertensive treatment. Although the difference during treatment still tended to increase with the height of pressure, the relationship was no longer statistically significant. Differences

in DBP were more or less constant, regardless of age, gender, severity of hypertension, or treatment status.

The most important clinical consequence of the above is that HBPM can largely eliminate the white coat effect, which is defined as an elevation of BP measured in the office compared to either ABPM or HBPM⁴⁸. Detection of the white coat effect is relevant to avoid overestimation of daily BP and unnecessary drug prescription. Because the white coat effect also increases with age⁴⁹ and is more related to untreated than to treated hypertension⁵⁰, HBPM seems to be particularly suitable to assess elderly people with hypertension. Although HBPM may not detect the same patients with the white coat effect as ABPM would², it serves at least the purpose of being a reasonable screening test for that phenomenon.

Still, a word of caution is in order because most studies that addressed HBPM in relation to OBPM used different devices for both methods; OBPM was usually assessed with manual mercury sphygmomanometers (auscultatory method), which carries the risk of observer bias due to, for example, hearing loss, impaired ability to react, and digit preference^{31,51,52}. On the other hand, HBPM was commonly performed with automatic or semiautomatic devices that used an oscillometric method to record the pressure. This may at least in part explain some of the differences between OBPM and HBPM. Additionally, most studies from Table 9.5 that addressed drug efficacy using HBPM and OBPM showed a larger decline in OBPM after treatment as compared with HBPM. Such differences could be due to the physician expecting a decline in BP after drug administration. This assumption is supported by the study of Vaur *et al.*³¹ who showed a decline in OBPM after treatment while the patient was using a placebo whereas this effect was absent in HBPM. Therefore, in order to exclude measurement bias in future clinical trials, OBPM and HBPM should be performed with the same device, preferably an automatic one⁵³. In the ongoing Home versus Office blood pressure MEasurement: Reduction of Unnecessary treatment Study (HOMERUS)⁵⁴, this approach has already been adopted.

HBPM and assessment of drug efficacy

The possibility of HBPM to obtain multiple measurements within a relatively short period of time makes the technique particularly useful to determine drug efficacy^{21,30,32}. As an index of efficacy, the morning-to-evening ratio has been introduced as an alternative for the “trough-to-peak ratio”, which is used with ABPM⁵⁵. With respect to the morning-to-evening ratio, one assumes that if medication is taken at a 24-h interval, the trough is reached just before the new medication is taken after 24 h in the morning, while 12 h earlier in the evening, the full effect of the drug can be expected (the peak).

HBPM and cardiovascular prognosis

Although only a few studies have addressed the relationship between HBPM and TOD, they are consistent in their results. Clearly, HBPM is superior to OBPM and comparable to ABPM in predicting cardiac as well as renal damage^{33,36}. As far as long-term cardiovascular prognosis is concerned, data also indicate that HBPM is the better predictor of outcome when compared to OBPM. For instance, the Ohasama study³⁸ clearly established a relationship between HBPM and mortality risk. When home BP values and screening BP values from this population study were simultaneously incorporated into a Cox model, only the average of multiple (more than three) home systolic BP values was significantly and strongly related to cardiovascular mortality risk. The average of the two initial home BP values was also better related to mortality risk than were the screening BP values. More recently, the same investigators presented their ten-year follow-up data⁴⁰, which indicated that the predictive value of HBP increases progressively with the number of measurements. When at least 14 measurements are obtained, HBPM shows a 35% increase in the risk of stroke per 10 mmHg elevation in BP. Nevertheless, even if one considers only initial HBP values (one measurement), stroke risk is better predicted by HBPM than by OBPM.

Despite some limitations of this study (other risk factors were ignored in the analysis, there was a higher overall mortality from cerebrovascular disease in Ohasama than in the rest of the country, and an arbitrarily chosen end point was used for determining acceptable risk), this is an important long-term follow-up study linking HBPM to cerebrovascular risk. The study also suggested that the correlation between home DBP and mortality is nonlinear (U-shaped curve) and that a very low DBP may be associated with increased mortality as well.

Conclusions

Although more research is needed, several arguments already speak in favour of implementing HBPM into daily clinical practice. First of all, it eliminates the white coat effect and allows identification of patients with white coat hypertension. Second, it offers the possibility to obtain multiple readings under standardised conditions with little measurement variability. This increases knowledge of usual BP value in such conditions as borderline hypertension^{28,56}, type II diabetes mellitus^{57,58}, and older age^{35,59-61}. In addition, it allows better judgment of drug efficacy^{21,24,26,29-32}. Third, HBPM data correlate better than OBPM values with TOD, in particular left ventricular hypertrophy^{33,36,37,58}, with cardiovascular events³⁹, and with cardiovascular mortality^{38,39}. The predictive power of HBPM increases with the number of measurements and should perhaps be based on the average of at least 14 data points⁴⁰. Finally, HBPM may increase patient's awareness of hypertension and compliance with drug

treatment, potentially leading to reduced mortality and costs⁶². In line with this supposition, a recent meta-analysis by Cappuccio *et al.*⁶³ showed that subjects using HBPM had lower BP values and were more likely to achieve their target BP value than subjects without HBPM.

In practice, many factors can influence HBPM. It is important, therefore, that established guidelines for procedures of self-monitoring of BP^{64,65} are meticulously followed and that patients receive extensive instruction from a well-trained nurse or physician⁶⁶. Recordings must be taken with devices⁶⁷⁻⁷⁵ that have been validated according to AAMI⁵, BHS⁴ and/or ESH⁶ standards (Table 9.6). Moreover, BP devices should be memory-equipped in order to prevent reporting bias⁷⁶. Because manual devices, which require the patient to inflate the cuff and/or to determine BP himself, are subject to the same forms of measurement bias as office recordings, automated ones are to be preferred.

Table 9.6 List of blood pressure monitors suitable for self-measurement and validated according to BHS, AAMI and/or ESH criteria.

Reference	Device
67	Omron HEM 705-CP
68	Microlife 3BTO-A
68	Microlife 3AG1
69	Omron M5-I
69	Omron 705 CPII
69	Omron 705IT
70	Omron MIT
71	UA-779/631
72	UA-787
73	Omron M4
74	UA-767
75	UA-774 (UA-767 Plus)

AAMI = Association for the Advancement of Medical Instrumentations; BHS = British Hypertension Society; ESH = European Society of Hypertension.

Notwithstanding all advantages, HBPM also has some limitations. First of all, the HBPM technique, like ABPM, is less suitable in subjects with large arm sizes for whom no appropriate cuff is available, in those with an irregular pulse, or when there is reason to suspect vascular stiffening. Indeed, almost all validated HBPM devices employ the oscillometric technique, which may yield results that differ substantially from BP readings taken with a sphygmomanometer. This is particularly true in elderly patients and those with diabetes^{77,78}. Second, ABPM is still superior for measuring BP at predetermined times without any influence of the patient, to record BP during daily routine or during the night and to ascertain whether a drug is effective

during the early morning surge. However, because HBPM is less expensive and less inconvenient for the patient, it can serve as a reliable addition to OBPM, although the latter should not be abandoned yet^{23,79}. Moreover, there is already an HBPM device available that is able to measure BP during sleep at predetermined times⁸⁰. Third, HBPM should not be recommended for subjects with pre-eclampsia because both the auscultatory and oscillometric methods have shown to be inappropriate in this situation⁸¹. Fourth, it should be realised that certain aspects of HBPM need further research, especially because the recently published Treatment of Hypertension based on home or Office blood Pressure (THOP) trial showed that adjustment of antihypertensive treatment based on HBPM instead of OBPM led to less intensive drug treatment but also to less BP control⁸². Therefore, until this subject has been investigated further, treatment decisions based on HBPM alone should be taken cautiously. Finally, because regular subjects require at least 20 min of instruction²⁸ before understanding the procedure, HBPM may not be appropriate for every patient because of its complexity. Additionally, HBPM should also be discouraged when it causes anxiety or induces self-modification of treatment.

Still, due to an ever-increasing workload for physicians, it seems to be only a matter of time before people measure their BP at home and transmit it through the internet to the hospital, instead of visiting the doctor at the clinic. This modern approach of hypertension management is already put into practice at the HOMED-BP trial⁸³.

References

1. British Hypertension Society. Available at: www.bhs.org. Accessed July 17, 2005.
2. Stergiou GS, Zourbaki AS, Skeva, II, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *Am J Hypertens* 1998;11:820-7.
3. Omvik P, Gerhardsen G. The Norwegian office-, home-, and ambulatory blood pressure study (NOHA). *Blood Press* 2003;12:211-9.
4. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, Jamieson M, Altman D, Bland M, Atkins N. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens* 1990;8:607-19.
5. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, Sheps SG. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension* 1993;21:504-9.
6. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waeber B, Palatini P, Gerin W. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit* 2002;7:3-17.
7. Rothman J. *Modern Epidemiology*. 1986;183-185.
8. Celis H, De Cort P, Fagard R, Thijs L, Staessen JA. For how many days should blood pressure be measured at home in older patients before steady levels are obtained? *J Hum Hypertens* 1997;11:673-7.
9. Stergiou GS, Skeva, II, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? *J Hypertens* 1998;16:725-31.
10. Garcia-Vera MP, Sanz J. How many self-measured blood pressure readings are needed to estimate hypertensive patients' "true" blood pressure? *J Behav Med* 1999;22:93-113.
11. Imai Y, Satoh H, Nagai K, Sakuma M, Sakuma H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N, Yabe T, Nishiyama A, Nakatsuka H, Koyama T, Abe K. Characteristics of a community-based distribution of home blood pressure in Ohasama in northern Japan. *J Hypertens* 1993;11:1441-9.
12. de Gaudemaris R, Chau NP, Mallion JM. Home blood pressure: variability, comparison with office readings and proposal for reference values. Groupe de la Mesure, French Society of Hypertension. *J Hypertens* 1994;12:831-8.
13. Stergiou GS, Thomopoulou GC, Skeva, II, Mountokalakis TD. Home blood pressure normalcy: the Didima study. *Am J Hypertens* 2000;13:678-85.
14. Thijs L, Staessen JA, Celis H, de Gaudemaris R, Imai Y, Julius S, Fagard R. Reference values for self-recorded blood pressure: a meta-analysis of summary data. *Arch Intern Med* 1998;158:481-8.
15. Thijs L, Staessen JA, Celis H, Fagard R, De Cort P, de Gaudemaris R, Enstrom I, Imai Y, Julius S, Menard J, Mion D, Palatini P, Rosenfeld J, Shapiro D, Spence D, Stergiou G. The international database of self-recorded blood pressures in normotensive and untreated hypertensive subjects. *Blood Press Monit* 1999;4:77-86.
16. Tsuji I, Imai Y, Nagai K, Ohkubo T, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Proposal of reference values for home blood pressure measurement: prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am J Hypertens* 1997;10:409-18.
17. Weisser B, Grune S, Burger R, Blickenstorfer H, Iseli J, Michelsen SH, Opravil R, Rageth S, Sturzenegger ER, Walker P, Widmer W, Vetter W. The Dubendorf Study: a population-based investigation on normal values of blood pressure self-measurement. *J Hum Hypertens* 1994;8:227-31.
18. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens* 1995;13:1377-90.

19. Bobrie G, Day M, Tugaye A, Chatellier G, Menard J. Self blood pressure measurement at home. *Clin Exp Hypertens* 1993;15:1109-19.
20. Cuspidi C, Michev I, Meani S, Salerno M, Valerio C, Fusi V, Bertazzoli G, Magrini F, Zanchetti A. Left ventricular hypertrophy in treated hypertensive patients with good blood pressure control outside the clinic, but poor clinic blood pressure control. *J Hypertens* 2003;21:1575-81.
21. Fernandez-Gonzalez R, Gomez-Pajuelo C, Gabriel R, de La Figuera M, Moreno E, of The Verapamil-Frequency R. Effect of verapamil on home self-measurement of blood pressure and heart rate by hypertensive patients. Verapamil-Frequency Research Group. *Blood Press Monit* 2000;5:23-30.
22. Hond ED, Celis H, Fagard R, Keary L, Leeman M, O'Brien E, Vandenhoven G, Staessen JA. Self-measured versus ambulatory blood pressure in the diagnosis of hypertension. *J Hypertens* 2003;21:717-22.
23. Jula A, Puukka P, Karanko H. Multiple clinic and home blood pressure measurements versus ambulatory blood pressure monitoring. *Hypertension* 1999;34:261-6.
24. Leeman MJ, Lins RL, Sternon JE, Huberlant BC, Fassotte CE. Effect of antihypertensive treatment on office and self-measured blood pressure: the Autodil study. *J Hum Hypertens* 2000;14:525-9.
25. Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood-pressure control in the hypertensive population. *Lancet* 1997;349:454-7.
26. Mengden T, Binswanger B, Spuhler T, Weissner B, Vetter W. The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening. *J Hypertens* 1993;11:1403-11.
27. Mengden T, Schwartzkopff B, Strauer BE. What is the value of home (self) blood pressure monitoring in patients with hypertensive heart disease? *Am J Hypertens* 1998;11:813-9.
28. Nesbitt SD, Amerena JV, Grant E, Jamerson KA, Lu H, Weder A, Julius S. Home blood pressure as a predictor of future blood pressure stability in borderline hypertension. The Tecumseh Study. *Am J Hypertens* 1997;10:1270-80.
29. Ragot S, Genes N, Vaur L, Herpin D. Comparison of three blood pressure measurement methods for the evaluation of two antihypertensive drugs: feasibility, agreement, and reproducibility of blood pressure response. *Am J Hypertens* 2000;13:632-9.
30. Stergiou GS, Efstathiou SP, Skeva, II, Baibas NM, Kalkana CB, Mountokalakis TD. Assessment of drug effects on blood pressure and pulse pressure using clinic, home and ambulatory measurements. *J Hum Hypertens* 2002;16:729-35.
31. Vaur L, Dubroca II, Dutrey-Dupagne C, Genes N, Chatellier G, Bouvier-d'Yvoire M, Elkik F, Menard J. Superiority of home blood pressure measurements over office measurements for testing antihypertensive drugs. *Blood Press Monit* 1998;3:107-14.
32. Zannad F, Vaur L, Dutrey-Dupagne C, Genes N, Chatellier G, Elkik F, Menard J. Assessment of drug efficacy using home self-blood pressure measurement: the SMART study. Self Measurement for the Assessment of the Response to Trandolapril. *J Hum Hypertens* 1996;10:341-7.
33. Tsunoda S, Kawano Y, Horio T, Okuda N, Takishita S. Relationship between home blood pressure and longitudinal changes in target organ damage in treated hypertensive patients. *Hypertens Res* 2002;25:167-73.
34. Campo C, Fernandez G, Gonzalez-Esteban J, Segura J, Ruilope LM. Comparative study of home and office blood pressure in hypertensive patients treated with enalapril/HCTZ 20/6 mg: the ESPADA study. *Blood Press* 2000;9:355-62.
35. Mallion JM, Genes N, Vaur L, Clerson P, Vaisse B, Bobrie G, Chatellier G. Blood pressure levels, risk factors and antihypertensive treatments: lessons from the SHEAF study. *J Hum Hypertens* 2001;15:841-8.
36. Mule G, Caimi G, Cottone S, Nardi E, Andronico G, Piazza G, Volpe V, Federico MR, Cerasola G. Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk* 2002;9:123-9.
37. Shimada K, Kario K, Umeda Y, Hoshida S, Hoshida Y, Eguchi K. Early morning surge in blood pressure. *Blood Press Monit* 2001;6:349-53.

38. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998;16:971-5.
39. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342-9.
40. Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsumi K, Satoh H, Imai Y. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004;22:1099-104.
41. Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, et al. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985;313:1315-22.
42. Muller JE, Ludmer PL, Willich SN, Toftler GH, Aylmer G, Kiangos I, Stone PH. Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987;75:131-8.
43. Marler JR, Price TR, Clark GL, Muller JE, Robertson T, Mohr JP, Hier DB, Wolf PA, Caplan LR, Foulkes MA. Morning increase in onset of ischemic stroke. *Stroke* 1989;20:473-6.
44. Kario K, Shimada K, Pickering TG. Clinical implication of morning blood pressure surge in hypertension. *J Cardiovasc Pharmacol* 2003;42 Suppl 1:S87-91.
45. Brook RD. Home blood pressure: accuracy is independent of monitoring schedules. *Am J Hypertens* 2000;13:625-31.
46. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Luscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 2003;21:1779-86.
47. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004;328:634-40.
48. Pickering TG, Gerin W, Schwartz AR. What is the white-coat effect and how should it be measured? *Blood Press Monit* 2002;7:293-300.
49. Mansoor GA, McCabe EJ, White WB. Determinants of the white-coat effect in hypertensive subjects. *J Hum Hypertens* 1996;10:87-92.
50. Stergiou GS, Efstathiou SP, Argyraki CK, Roussias LG, Mountokalakis TD. White coat effect in treated versus untreated hypertensive individuals: a case-control study using ambulatory and home blood pressure monitoring. *Am J Hypertens* 2004;17:124-8.
51. McManus RJ, Mant J, Hull MR, Hobbs FD. Does changing from mercury to electronic blood pressure measurement influence recorded blood pressure? An observational study. *Br J Gen Pract* 2003;53:953-6.
52. Bruce NG, Shaper AG, Walker M, Wannamethee G. Observer bias in blood pressure studies. *J Hypertens* 1988;6:375-80.
53. Myers MG. Blood pressure measurement and the guidelines: a proposed new algorithm for the diagnosis of hypertension. *Blood Press Monit* 2004;9:283-6.
54. Verberk WJ, Kroon AA, Kessels AG, Dirksen C, Nelemans PJ, Lenders JW, Thien TA, van Montfrans GA, Smit AJ, de Leeuw PW. Home versus Office blood pressure MEasurements: Reduction of Unnecessary treatment Study: rationale and study design of the HOMERUS trial. *Blood Press* 2003;12:326-33.
55. Menard J, Chatellier G, Day M, Vaur L. Self-measurement of blood pressure at home to evaluate drug effects by the trough: peak ratio. *J Hypertens Suppl* 1994;12:S21-5.
56. Amerena J, Nesbitt S, Krause L, Grant E, Lu H, Julius S. Trends in left ventricular function over three years in the Tecumseh Study. *Blood Press* 1997;6:262-8.
57. Masding MG, Jones JR, Bartley E, Sandeman DD. Assessment of blood pressure in patients with Type 2 diabetes: comparison between home blood pressure monitoring, clinic blood pressure measurement and 24-h ambulatory blood pressure monitoring. *Diabet Med* 2001;18:431-7.

58. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 2002;25:2218-23.
59. Sega R, Cesana G, Milesi C, Grassi G, Zanchetti A, Mancia G. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. *Hypertension* 1997;30:1-6.
60. Broege PA, James GD, Pickering TG. Management of hypertension in the elderly using home blood pressures. *Blood Press Monit* 2001;6:139-44.
61. Okumiya K MK, Wada T, Fujisawa M, Osaki Y, Doi Y, Yasuda N, Ozawa T. A U-shaped association between home systolic blood pressure and four-year mortality in community-dwelling older men. *J Am Geriatr Soc* 1999;47:1477-8.
62. Ashida T, Sugiyama T, Okuno S, Ebihara A, Fujii J. Relationship between home blood pressure measurement and medication compliance and name recognition of antihypertensive drugs. *Hypertens Res* 2000;23:21-4.
63. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. *BMJ* 2004;329:145.
64. Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF, Poulter NR, Russell G. British Hypertension Society guidelines for hypertension management 1999: summary. *BMJ* 1999;319:630-5.
65. Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K. Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003;26:771-82.
66. Campbell NR, Milkovich L, Burgess E, McKay DW. Self-measurement of blood pressure: accuracy, patient preparation for readings, technique and equipment. *Blood Press Monit* 2001;6:133-8.
67. Artigao LM, Llavorador JJ, Puras A, Lopez Abril J, Rubio MM, Torres C, Vidal A, Sanchis C, Divison JA, Naharro F, Caldevilla D, Fuentes G. [Evaluation and validation of Omron Hem 705 CP and Hem 706/711 monitors for self-measurement of blood pressure]. *Aten Primaria* 2000;25:96-102.
68. Cuckson AC, Reinders A, Shabeeh H, Shennan AH. Validation of the Microlife BP 3BTO-A oscillometric blood pressure monitoring device according to a modified British Hypertension Society protocol. *Blood Press Monit* 2002;7:319-24.
69. El Assaad MA, Topouchian JA, Asmar RG. Evaluation of two devices for self-measurement of blood pressure according to the international protocol: the Omron M5-I and the Omron 705IT. *Blood Press Monit* 2003;8:127-33.
70. Golara M, Jones C, Randhawa M, Shennan AH. Inflationary oscillometric blood pressure monitoring: validation of the OMRON-MIT. *Blood Press Monit* 2002;7:325-8.
71. Longo D, Bertolo O, Toffanin G, Frezza P, Ralatini P. Validation of the A&D UA-631 (UA-779 Life Source) device for self-measurement of blood pressure and relationship between its performance and large artery compliance. *Blood Press Monit* 2002;7:243-8.
72. Longo D, Toffanin G, Garbelotto R, Zaetta V, Businaro L, Palatini P. Performance of the UA-787 oscillometric blood pressure monitor according to the European Society of Hypertension protocol. *Blood Press Monit* 2003;8:91-5.
73. Naschitz JE, Loewenstein L, Lewis R, Keren D, Gaitini L, Tamir A, Yeshurun D. Accuracy of the OMRON M4 automatic blood pressure measuring device. *J Hum Hypertens* 2000;14:423-7.
74. Rogoza AN, Pavlova TS, Sergeeva MV. Validation of A&D UA-767 device for the self-measurement of blood pressure. *Blood Press Monit* 2000;5:227-31.
75. Verdecchia P, Angeli F, Poeta F, Reboldi GP, Borgioni C, Pittavini L, Porcellati C. Validation of the A&D UA-774 (UA-767Plus) device for self-measurement of blood pressure. *Blood Press Monit* 2004;9:225-9.
76. Mengden T, Hernandez Medina RM, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens* 1998;11:1413-7.

77. van Popele NM, Bos WJ, de Beer NA, van Der Kuip DA, Hofman A, Grobbee DE, Witteman JC. Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer. *Hypertension* 2000;36:484-8.
78. Raptis AE, Spring MW, Viberti G. Comparison of blood pressure measurement methods in adult diabetics. *Lancet* 1997;349:175-6.
79. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B, Lonati L, Magrini F, Zanchetti A. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004;22:273-80.
80. Chonan K, Kikuya M, Araki T, Fujiwara T, Suzuki M, Michimata M, Hashimoto J, Ohkubo T, Hozawa A, Yamamoto N, Miyawaki Y, Matsubara M, Imai Y. Device for the self-measurement of blood pressure that can monitor blood pressure during sleep. *Blood Press Monit* 2001;6:203-5.
81. Natarajan P, Shennan AH, Penny J, Halligan AW, de Swiet M, Anthony J. Comparison of auscultatory and oscillometric automated blood pressure monitors in the setting of preeclampsia. *Am J Obstet Gynecol* 1999;181:1203-10.
82. Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G, O'Brien ET. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA* 2004;291:955-64.
83. Fujiwara T, Nishimura T, Ohkuko T, Imai Y. Rationale and design of HOMED-BP Study: hypertension objective treatment based on measurement by electrical devices of blood pressure study. *Blood Press Monit* 2002;7:77-82.

Chapter 10

General discussion

General discussion

Since blood pressure markedly fluctuates during the day, it is impossible to diagnose hypertension on the basis of one conventional measurement at a single visit to the physician's office. Although ambulatory blood pressure monitoring (ABPM) allows a better estimate of the true blood pressure level, this technique is not suitable for routine clinical practice. Therefore, it would be a welcome addition if patients could measure their blood pressure on multiple occasions at home. Until recently, self blood pressure measurement (SBPM), also referred to as home blood pressure measurement (HBPM), has been the subject of scepticism, as its reliability and its applicability have not been firmly established for clinical use. In particular, concerns were voiced about the usefulness of this method in routine daily patient care. In other words, will the results of SBPM ever influence clinical decision making? Indeed, one may legitimately ask whether SBPM has anything to add if the decision to initiate or alter antihypertensive treatment would always be taken on the basis of office measurements. From an even more practical point of view, there is still some uncertainty about how often self-measurements should be taken and how reliable these are. This lack of practical knowledge prompted us to set up a study that would be able to answer at least some of these questions. This resulted in the *Home versus Office MEasurement: Reduction of Unnecessary treatment Study* (HOMERUS). The results of this trial formed the core of the present thesis.

In chapter 2 of this thesis we described the protocol of HOMERUS. Basically, it was a multicentre randomised clinical trial that investigated whether treatment based on SBPM would lead to reduced medication use without leading to worse blood pressure control or target organ damage. Accordingly, the study population was divided into two treatment groups: the Self Pressure (SP) group and the Office Pressure (OP) group. Antihypertensive drug treatment was adjusted according to a standardised schedule based on either SBPM (average of six measurements per day for seven days) for the SP group or office blood pressure measurement (OBPM; average of three measurements at the physician's office) for the OP group. If blood pressure exceeded 139 mmHg systolic and/or 89 mmHg diastolic, treatment was intensified by one step, if it came below 120 mmHg systolic and 80 mmHg diastolic, treatment was reduced by one step. In a way, this approach may be criticised because patients in the OP group had no SBPM and, therefore, one may say that the groups were not comparable (as they were, for instance, in the THOP trial). However, we deliberately chose this design to be able to compare a treatment strategy based on SBPM with present-day standard care (in which SBPM has no or only a minor role).

In order to obtain treatment groups, which were similar for characteristics that may influence blood pressure values, patients were dynamically randomised by means of a minimisation procedure. The details of this randomisation procedure have been described in chapter 3, together with the baseline characteristics of the study population. We have compared the method of minimisation with two other randomisation methods: non-stratified and stratified randomisation, which were performed post-hoc. This comparison clearly demonstrated that several patient characteristics have a profound influence on blood pressure. Since blood pressure was one of the most important outcomes in this trial, it was important that this characteristic was well-balanced over the two treatment groups. A procedure of non-stratified randomisation, however, would have led to a difference in diastolic 24-h ambulatory blood pressure measurement (ABPM). Stratified randomisation would have resulted in similar 24-h ABPM values as compared to minimisation, but in practice stratified randomisation has the disadvantage that the amount of outcome factors for which can be randomised is limited. The procedure of minimisation provided excellent randomisation and, therefore, turned out to be highly appropriate for use in clinical trials such as HOMERUS. Accordingly, we would strongly advocate the use of a minimisation technique in future trials with a size comparable to that of HOMERUS.

Altogether, we included 430 mild-to-moderate hypertensive subjects (55% males) with a mean age of 55 years and a body mass index of 28 kg/m^2 (see **Chapter 4**). By and large, the trial ran a smooth course and major obstacles were encountered. It proved possible to keep the patients in the trial for a year and we accomplished to retain as much as possible the blinded character of the treatment. The final results indicated that adjustment of antihypertensive therapy based on SBPM reduces the number of necessary antihypertensive drugs without loss of OBPM control, increase of target organ damage or increase in the number of refractory hypertensives. Consequently, this also led to a reduction in costs for treatment that amounted to \$853 per 100 patients for one month. In addition, patients of the SP group were more likely to reach the target blood pressure value compared to patients of the OP group. Twenty-four ABPM fell to a greater extent in the OP than in the SP group, which indicates that the threshold values for SBPM as were chosen in the present study to base antihypertensive treatment on were not appropriate. This indicates that treatment probably should be based on lower threshold values for SBPM and thus threshold values such as momentarily recommended by the ESH (135 mmHg for systolic and 85 mmHg for diastolic) seems fully justified¹. Except for the THOP-trial (discussed in Chapter 4 as well), there are no other data in the literature which are comparable to ours. Thus, HOMERUS may pave the way for other investigators using different treatment designs to further evaluate the place of SBPM as a guide to treatment.

As indicated in chapter 5 we took advantage of the HOMERUS-database to study among the patients from the SP group, which SBPM correlated best with 24-h ABPM. As has been shown in former studies, the first SBPM value of each triplicate session always was higher than subsequent ones from the first until the seventh day. The average first-day SBPM result was higher than the average values thereafter. The one that best correlated with 24-h ABPM was the average SBPM value obtained from day 3 through day 7, omitting the first measurement of each triplicate session. However, the SBPM value calculated from day 3 until 5 provided similar results. Thus, five days of measurement suffice as well to optimally establish blood pressure values using SBPM. Patient characteristics considerably influenced the correlation of SBPM with ABPM. Especially, patients with lower systolic OBPM (<165 mmHg) had significantly higher correlations than those with higher systolic OBPM and younger patients (<50 years) had correlations, which were significantly higher than the elderly. In addition, females had higher correlations in the morning than in the evening, while males showed the opposite pattern. For this reason we conclude that, for recommendations regarding the number of necessary SBPMs, several patient characteristics should be taken into account. Elderly or patients with high office blood pressure values should perform more SBPMs than younger patients or those with lower OBPM values. From a practical point of view, one could consider to recommend just morning measurements for women and evening measurements for men. However, this only can be recommended after patients have first performed both morning and evening measurements so that the treating physician is familiar with these values.

In chapter 6, we tried to reveal the identity of masked hypertension, a rather new phenomenon of which the persistence and the origin are still uncertain. Masked hypertension is considered to be present when blood pressure in the physician's office is normal but elevated elsewhere. Until now, it was uncertain whether masked hypertension deserves special attention as a discrete identity or that it is caused by an occasionally low OBPM while SBPM or daytime ABPM are high. According to the European Society of Hypertension (ESH) guidelines⁵ masked hypertension should be defined as an OBPM value lower than 140 mmHg systolic and 90 mmHg diastolic while SBPM or daytime ABPM is equal to or greater than 135 mmHg systolic and/or 85 mmHg diastolic. However, this definition only classifies patients with blood pressure values around these upper limits while a masked hypertensive effect may occur in patients with higher blood pressure values as well. Therefore we proposed, and evaluated, two alternative definitions: first, the SBPM or daytime ABPM value is at least 5 mmHg systolic and 3 mmHg diastolic higher than the OBPM value: the 5/3 definition. Second, the SBPM or daytime ABPM value is at least 10 mmHg systolic and 6 mmHg diastolic higher than the OBPM value: the 10/6 definition. Our results indicate that with 8 subsequent occasions of blood

pressure measurement more than 40% of all patients is at least once classified as having masked hypertension according to the ESH and 5/3 definition. Overall, masked hypertension usually was the result of an exceptionally low OBPM value at one occasion. Despite the fact that in this study masked hypertension led to (increased) antihypertensive treatment, OBPM values were usually higher again at the next occasion. Therefore, the number of patients, who repeatedly had masked hypertension, was small. According to the 5/3 and the 10/6 definitions the prevalence of masked hypertension remained constant, which means that the underlying cause is at least independent of the blood pressure level or antihypertensive treatment. Therefore, we concluded that masked hypertension is the result of an exceptionally low OBPM value at one particular occasion and not a discrete clinical entity. In order to exclude masked hypertension, SBPM should be implemented into clinical healthcare.

Current knowledge of masked hypertension is still limited (see Chapter 7). Available data show that the prevalence of masked hypertension varies enormously among studies which is probably related to widely varying methods to detect the condition and the way subjects have been selected. Since masked hypertension is associated with a high degree of target organ damage and therefore proves its clinical significance, more research should be directed towards this phenomenon in future. We make a strong plea for reaching consensus on the definition and determination of masked hypertension in order to guarantee homogeneity among future studies regarding this topic.

As a next step, we also wanted to investigate the persistence of the opposite phenomenon, which is white coat hypertension (WCH) and the white coat effect (WCE). The results of this study, described in chapter 8, showed that, on eight measurement occasions, almost 75% of all patients had once or more a substantial WCE (defined as an OBPM value that is at least 20 mmHg systolic or 10 mmHg diastolic higher than SBPM or daytime ABPM) and 57% had at least once WCH. On three or more BP measurement occasions one-third of all patients consistently had substantial WCE and 14% consistently had WCH. Therefore, we conclude that for some patients WCH or the WCE does not disappear with frequent OBPMs, which pleads for implementation of SBPM into regular care. Repeated occasions of SBPM prevent erroneous classification of patients, as it may occur either due to the WCE or masked hypertension.

In chapter 9 we have presented the results from a systematic literature search of studies that dealt with the subject of SBPM at home. In this review we focussed on the following questions: 1) how many measurements are needed to estimate a patient's usual blood pressure? 2) what are normal values for SBPM? 3) how does SBPM affect antihypertensive treatment? 4) to what extent can SBPM predict prognosis? In order to find appropriate answers, we selected all available observational studies on SBPM from 1992 onwards if they met the following criteria: 1) SBPM was performed with a validated device,

2) SBPM was described in sufficient detail, and 3) the paper clearly described how SBPM values were calculated. After pooling the data from the literature, we found that for a reliable SBPM value one should, at least, perform two duplicate measurements per day (2 in the morning and 2 in the evening) for 3 consecutive days. Data from the first day should be discarded, as these are consistently higher than on subsequent days. In accordance with the recommendations of the European Society of Hypertension (ESH) and the British Hypertension Society (BHS) our findings confirmed that it is appropriate to set the upper normal limits of SBPM at 135 systolic and 85 mmHg diastolic. This review confirmed that SBPM is an appropriate tool for assessment of drug efficacy⁶⁻¹² and that it is superior to OBPM in predicting cardiac and renal damage, stroke and cerebrovascular disease¹³⁻¹⁶. In addition, our pooled analyses showed that the difference in systolic blood pressure between OBPM and SBPM in untreated patients tends to be greater in males than in females, and to increase with the height of blood pressure and with age. Other findings were as follows:

- SBPM eliminates the white coat effect and allows identification of patients with white coat hypertension.
- SBPM offers the possibility to obtain multiple readings under standardised conditions with little measurement variability. This increases knowledge of usual blood pressure values in conditions as borderline hypertension^{17,18}, type 2 diabetes mellitus^{19,20} and older age²¹⁻²⁴.
- SBPM increases patient's awareness of hypertension and compliance with drug treatment, potentially leading to reduced mortality and costs²⁵.
- SBPM increases the chance for patients of reaching their target blood pressure²⁶.

Our interpretation of the available data led to the following recommendations with regard to the application of SBPM:

- Established guidelines for procedures of self-monitoring of blood pressure^{27,28} should be followed meticulously.
- Patients should receive extensive instruction from a well-trained nurse or physician²⁹.
- Recordings must be taken with devices that have been validated according to Association for the Advancement of Medical Instrumentation (AAMI)³⁰, BHS³¹ and/or ESH³² standards.
- Blood pressure measurement devices should be memory-equipped in order to prevent reporting bias³³.
- Since manual devices, which require the patient to inflate the cuff and/or to determine blood pressure himself, are subject to the same forms of measurement bias as office recordings, automated ones are to be preferred.

Notwithstanding its advantages, SBPM has also some limitations:

- The SBPM technique, like ABPM, is less suitable in subjects with unusual arm circumferences for whom no appropriate cuff is available.
- Since most devices utilise the oscillometric technique, patients with an irregular pulse or extremely increased vascular stiffening cannot be measured, which concerns the elderly or subjects with diabetes mellitus in particular^{34,35}.
- ABPM is still superior when blood pressure has to be measured without any influence of the patient, e.g., during daily routine or during the night, or to ascertain whether a drug is effective during the early morning surge.
- SBPM may not be appropriate for every patient because some cannot handle the apparatus technically.
- SBPM may cause anxiety or induction of self-modification of treatment.

What the present study adds

Since blood pressure is subject to variability, it is essential to perform multiple measurements in order to prevent misdiagnosis as illustrated in the cases of masked and white coat hypertension. When blood pressure was measured on more occasions, the persistence of masked hypertension was low. Therefore, masked hypertension can be detected when patients are measured on more OBPM occasions before antihypertensive treatment is instituted. Otherwise SBPM should be used in order to obtain a reliable estimate of a patient's blood pressure. The finding that WCH and the WCE were more reproducible on frequent measurement occasions indicates that OBPM alone is not enough to reveal these phenomenon and underscores the need for SBPM in treatment of hypertension.

For a reliable estimate of a patient's blood pressure, at least three days of measurements are necessary, each day containing duplicate morning and evening measurements. The average value should be calculated from day two and three. However, for an optimal and reproducible result, SBPM should be performed on at least five days, each day containing three morning and three evening measurements. The average blood pressure of days 3 to 5 should be taken, discarding the data from the first two days and the first measurement of each session. When patients are older it is advisable to let them perform a few more days of measurement.

Antihypertensive treatment can be based on SBPM at home without leading to differences in OBPM values but with slightly higher ABPM values. It will lead to a reduction in antihypertensive treatment and consequently to reduced healthcare costs. However, the higher ABPM values, at the end of the study for patients treated on SBPM values indicates that the thresholds values of 140

mmHg systolic and 90 mmHg diastolic were not appropriate. Therefore, in order to treat patients based on their SBPM values it seems to be recommendable to use lower threshold values such as presently recommended by the ESH of 135 mmHg for systolic and 85 mmHg for diastolic blood pressure. Since about one million subjects in the Netherlands are more or less bothered by hypertension the application of SBPM will have a large impact on society. Finally, due to increasing workload for physicians and improvement of automatic blood pressure measurement devices, self-measurement at home may improve blood pressure control without leading to additional burden in clinical healthcare.

Future research

The data of the HOMERUS trial can be taken as evidence that it is desirable to implement SBPM in clinical practice. However, for practical reasons this is not immediately possible, at least not in all patients. Nevertheless, we are inclined to recommend SBPM in particular for patients in whom there is doubt whether treatment should be started or not. At the same time, this is an important subject for further study. It is essential to know whether one can safely withhold treatment for some time, if SBPM yields low blood pressure values. Also, the relationship between SBPM data and prognosis needs further exploration. This also applies to the number of measurements for which we have found some solution for the time being but this needs to be linked to prognosis as well. Many other studies could follow HOMERUS, such as whether SBPM can replace (part of the) routine clinical visits to the doctor. Finally, the cost-effectiveness of SBPM needs to be scrutinised over longer periods of time.

Almost three millennia after the great Greek poet Homerus (Homer in the Anglo-Saxon literature) wrote his famous *Odyssey*, the trial that formed the core of this thesis truly has been an *Odyssey* through the largely unknown land of masked and overt hypertension with many tempting challenges and challenging temptations.

References

1. Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001;38:852-7.
2. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999;282:539-46.
3. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801.
4. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777-83.
5. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;23:697-701.
6. Fernandez-Gonzalez R, Gomez-Pajuelo C, Gabriel R, de La Figuera M, Moreno E, of The Verapamil-Frequency R. Effect of verapamil on home self-measurement of blood pressure and heart rate by hypertensive patients. Verapamil-Frequency Research Group. *Blood Press Monit* 2000;5:23-30.
7. Leeman MJ, Lins RL, Sternon JE, Huberlant BC, Fassotte CE. Effect of antihypertensive treatment on office and self-measured blood pressure: the Autodil study. *J Hum Hypertens* 2000;14:525-9.
8. Mengden T, Binswanger B, Spuhler T, Weisser B, Vetter W. The use of self-measured blood pressure determinations in assessing dynamics of drug compliance in a study with amlodipine once a day, morning versus evening. *J Hypertens* 1993;11:1403-11.
9. Vaur L, Dubroca II, Dutrey-Dupagne C, Genes N, Chatellier G, Bouvier-d'Yvoire M, Elkik F, Menard J. Superiority of home blood pressure measurements over office measurements for testing antihypertensive drugs. *Blood Press Monit* 1998;3:107-14.
10. Ragot S, Genes N, Vaur L, Herpin D. Comparison of three blood pressure measurement methods for the evaluation of two antihypertensive drugs: feasibility, agreement, and reproducibility of blood pressure response. *Am J Hypertens* 2000;13:632-9.
11. Stergiou GS, Baibas NM, Gantzarou AP, Skeva, II, Kalkana CB, Roussias LG, Mountokalakis TD. Reproducibility of home, ambulatory, and clinic blood pressure: implications for the design of trials for the assessment of antihypertensive drug efficacy. *Am J Hypertens* 2002;15:101-4.
12. Zannad F, Vaur L, Dutrey-Dupagne C, Genes N, Chatellier G, Elkik F, Menard J. Assessment of drug efficacy using home self-blood pressure measurement: the SMART study. Self Measurement for the Assessment of the Response to Trandolapril. *J Hum Hypertens* 1996;10:341-7.
13. Tsunoda S, Kawano Y, Horio T, Okuda N, Takishita S. Relationship between home blood pressure and longitudinal changes in target organ damage in treated hypertensive patients. *Hypertens Res* 2002;25:167-73.
14. Mule G, Cairni G, Cottone S, Nardi E, Andronico G, Piazza G, Volpe V, Federico MR, Cerasola G. Value of home blood pressures as predictor of target organ damage in mild arterial hypertension. *J Cardiovasc Risk* 2002;9:123-9.
15. Bobrie G, Genes N, Vaur L, Clerson P, Vaisse B, Mallion JM, Chatellier G. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med* 2001;161:2205-11.

16. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998;16:971-5.
17. Nesbitt SD, Amerena JV, Grant E, Jamerson KA, Lu H, Weder A, Julius S. Home blood pressure as a predictor of future blood pressure stability in borderline hypertension. The Tecumseh Study. *Am J Hypertens* 1997;10:1270-80.
18. Amerena J, Nesbitt S, Krause L, Grant E, Lu H, Julius S. Trends in left ventricular function over three years in the Tecumseh Study. *Blood Press* 1997;6:262-8.
19. Masding MG, Jones JR, Bartley E, Sandeman DD. Assessment of blood pressure in patients with Type 2 diabetes: comparison between home blood pressure monitoring, clinic blood pressure measurement and 24-h ambulatory blood pressure monitoring. *Diabet Med* 2001;18:431-7.
20. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 2002;25:2218-23.
21. Sega R, Cesana G, Milesi C, Grassi G, Zanchetti A, Mancia G. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. *Hypertension* 1997;30:1-6.
22. Mallion JM, Genes N, Vaur L, Clerson P, Vaisse B, Bobrie G, Chatellier G. Blood pressure levels, risk factors and antihypertensive treatments: lessons from the SHEAF study. *J Hum Hypertens* 2001;15:841-8.
23. Broege PA, James GD, Pickering TG. Management of hypertension in the elderly using home blood pressures. *Blood Press Monit* 2001;6:139-44.
24. Okumiyu K MK, Wada T, Fujisawa M, Osaki Y, Doi Y, Yasuda N, Ozawa T. A U-shaped association between home systolic blood pressure and four-year mortality in community-dwelling older men. *J Am Geriatr Soc* 1999;47:1477-8.
25. Ashida T, Sugiyama T, Okuno S, Ebihara A, Fujii J. Relationship between home blood pressure measurement and medication compliance and name recognition of antihypertensive drugs. *Hypertens Res* 2000;23:21-4.
26. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. *BMJ* 2004;329:145.
27. Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF, Poulter NR, Russell G. British Hypertension Society guidelines for hypertension management 1999: summary. *BMJ* 1999;319:630-5.
28. Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K. Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003;26:771-82.
29. Campbell NR, Milkovich L, Burgess E, McKay DW. Self-measurement of blood pressure: accuracy, patient preparation for readings, technique and equipment. *Blood Press Monit* 2001;6:133-8.
30. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, Sheps SG. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension* 1993;21:504-9.
31. O'Brien E, Petrie J, Littler W, de Swiet M, Padfield PL, O'Malley K, Jamieson M, Altman D, Bland M, Atkins N. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens* 1990;8:607-19.
32. O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, Mengden T, Imai Y, Waerber B, Palatini P, Gerin W. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit* 2002;7:3-17.
33. Mengden T, Hernandez Medina RM, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens* 1998;11:1413-7.

34. van Popele NM, Bos WJ, de Beer NA, van Der Kuip DA, Hofman A, Grobbee DE, Witteman JC. Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer. *Hypertension* 2000;36:484-8.
35. Raptis AE, Spring MW, Viberti G. Comparison of blood pressure measurement methods in adult diabetics. *Lancet* 1997;349:175-6.

Samenvatting

Samenvatting

Tot voor kort was zelfmeten van de bloeddruk sterk onderhevig aan scepsis voor wat betreft de betrouwbaarheid en bruikbaarheid van de daarmee verkregen resultaten. Echter, enig wantrouwen ten aanzien van bloeddrukmeting zoals momenteel wordt gedaan door de arts in de huisartsenpraktijk of kliniek, de zogenaamde conventionele bloeddrukmeting, zou minstens zo gerechtvaardigd zijn. Omdat de bloeddruk sterk varieert gedurende de dag is het onmogelijk om conclusies te trekken uit het resultaat van één enkele meting door de arts terwijl dit momenteel wel de gebruikelijke gang van zaken is. Bovendien hebben veel patiënten, ten tijde van de conventionele meting, een verhoogde bloeddruk in de aanwezigheid van een arts: het zogenaamde “witte jassen effect”. Het zou dan ook een welkome aanvulling zijn wanneer patiënten hun bloeddruk zelf zouden meten. Immers, met zelfmeting kunnen meerdere metingen verkregen worden zonder dat de patiënt last heeft van het witte jassen effect. Dit zal een beter beeld geven van de werkelijke bloeddruk waardoor de meest adequate behandeling kan worden gegeven. Omdat bij zelfmeting het witte jassen effect afwezig is, zal wellicht blijken dat de patiënt minder medicatie nodig heeft dan, op basis van de conventionele meting, door de arts is voorgeschreven.

Om dit te onderzoeken is een gerandomiseerd klinisch onderzoek gedaan met de naam HOMERUS wat staat voor “Home versus Office MEasurement a Reduction of Unnecessary treatment Study”. HOMERUS is een samenwerkingsproject van de academische ziekenhuizen van Maastricht, Nijmegen, Amsterdam (AMC), Groningen en diverse huisartsenpraktijken. Met data van deze studie zijn tevens aanvullende analyses gedaan om resterende vragen over thuismeting te beantwoorden.

Hoofdstuk 2 van dit proefschrift beschrijft het onderzoeksprotocol. HOMERUS had als voornaamste onderzoeksvraag of het behandelen van patiënten op basis van zelf gemeten bloeddrukwaarden leidt tot minder medicatiegebruik, zonder dat dit gepaard gaat met slechtere bloeddrukcontrole of meer orgaanschade.

Hiervoor werd de onderzoekspopulatie verdeeld in twee behandelgroepen: in de ene groep werd de behandeling tegen hoge bloeddruk gebaseerd op de bloeddrukwaarden verkregen door zelfmeting: de zelfmeetgroep, in de andere groep werd de behandeling gebaseerd op de conventionele methode, namelijk bloeddruk door de arts gemeten in de kliniek of praktijk: de controlegroep. Verdeling over deze twee groepen (randomiseren) werd gedaan met de methode genaamd “minimisatie”. Deze methode dient te voorkomen (minimaliseren) dat de twee patiëntengroepen verschillen in eigenschappen. Immers, wanneer twee patiëntengroepen verschillende eigenschappen hebben zou er een verschil in bloeddruk kunnen ontstaan terwijl dit niets te maken heeft met

datgene wat onderzocht wordt. Zo stijgt de bloeddruk bijvoorbeeld met de leeftijd en wanneer de ene patiëntengroep gemiddeld een hogere leeftijd zou hebben dan de andere groep zijn deze groepen niet meer vergelijkbaar omdat de aanvangswaarde van de bloeddruk, tenminste theoretisch, reeds verschilt. De nauwkeurigheid van de randomisatie methode is, samen met de karakteristieken van de deelnemende patiënten, uitvoerig beschreven in hoofdstuk 3 van dit proefschrift. In dit hoofdstuk werd de minimalisatie methode vergeleken met twee andere, veel gebruikte, randomisatie methoden: ongestratificeerde en gestratificeerde randomisatie. De minimalisatie methode kan het best uitgelegd worden aan de hand van een voorbeeld. Stel, een vrouw van 50 jaar oud, afkomstig uit een huisartsenpraktijk in Groningen, zonder orgaanschade en met inlooperperiode, moet worden ingedeeld in één van de twee behandelgroepen. In onderstaande tabel staan de eigenschappen waarvoor gerandomiseerd moet worden en het aantal, tot dan toe, geïnccludeerde patiënten met deze eigenschappen per behandelgroep. Om de behandelgroep voor deze patiënt te bepalen moeten corresponderende eigenschappen voor iedere groep worden opgeteld:

Dus voor de zelfmeetgroep is de som: $106+40+128+221+156+219=870$

En voor de controlegroep is de som: $104+45+129+221+157+221=877$

Tabel

Factor	Mogelijkheid	Zelfmeetgroep	Controlegroep	Volgende patiënt
Geslacht	Man	123	126	
	Vrouw	106	104	←
Regio	Maastricht	99	101	
	Nijmegen	47	38	
	Amsterdam	43	46	
	Groningen	40	45	←
Leeftijd	<40	22	23	
	40-60	128	129	←
	>60	79	78	
Orgaanschade	Ja	8	9	
	Nee	221	221	←
Centrum	Huisartsenpraktijk	156	157	←
	Kliniek	73	73	
Inlooperperiode	Ja	219	221	←
	Nee	10	9	

De patiënt zal worden ingedeeld in de behandelgroep met de laagste som, in dit geval betekent dat de zelfmeetgroep. Gestratificeerde randomisatie houdt in dat patiënten worden onderverdeeld in afzonderlijke vakken (strata) op basis van patiëtereigenschappen. De methode streeft erna om de twee behandelgroepen binnen deze strata zo gelijkwaardig mogelijk te verdelen. Bij

ongestratificeerde randomisatie heeft een patiënt evenveel kans om in één van de twee behandelgroepen terecht te komen.

Indien we zouden hebben gekozen voor de ongestratificeerde randomisatie methode zou dit, zoals uit een post-hoc analyse van onze gegevens blijkt, hebben geleid tot een verschil in hoogte van 24-uurs bloeddrukmeting tussen beide groepen en daarom is het gebruik van deze methode minder geschikt voor klinisch onderzoek. Gestratificeerde randomisatie daarentegen, leidde wel tot gelijke bloeddrukwaarden tussen beide groepen maar deze methode heeft als nadeel dat het aantal factoren, waarvoor gerangschikt kan worden, beperkt is. De minimalisatie methode leidde tot een optimale verdeling zonder deze beperking en is daarom uitermate geschikt voor klinische studies zoals het HOMERUS-onderzoek. Voor HOMERUS werden uiteindelijk 430 patiënten met hypertensie (hoge bloeddruk) en een gemiddelde leeftijd van 55 jaar onderzocht.

Hoofdstuk 4 omvat de resultaten van HOMERUS en daarmee het belangrijkste onderdeel van dit proefschrift. Deze resultaten tonen dat het behandelen van hoge bloeddruk gebaseerd op zelfmeting leidt tot minder medicatiegebruik, zonder dat dit gepaard gaat met slechtere bloeddrukwaarden zoals gemeten door de arts, of ontwikkeling van orgaanschade, in vergelijking tot de controlegroep. Dit resulteerde in een maandelijkse kostenbesparing in medicatie van \$853 per 100 patiënten voor de zelfmeetgroep ten opzichte van de controlegroep. Patiënten uit de zelfmeetgroep hadden echter wel een hogere 24-uurs bloeddruk dan patiënten uit de controlegroep. Hoewel het verschil in bloeddruk erg klein was (2 mmHg systolisch en 1 mmHg diastolisch) zou dit wel consequenties kunnen hebben voor de totale populatie. Het verdient dan ook aanbeveling om, wanneer patiënten behandeld worden op basis van zelfmeting, lagere bovengrenzen (bijvoorbeeld 135 mmHg systolisch en 85 mmHg diastolisch) in acht te nemen.

In hoofdstuk 5 is onderzocht hoe met behulp van zelfmeting een optimale bloeddrukwaarde verkregen kan worden. Hiervoor werden allerlei “zelf” bloeddrukwaarden, verkregen uit verschillende combinaties van dagen en metingen, gecorreleerd aan 24-uurs bloeddrukwaarden. Het doel van deze studie was te bepalen bij welke combinatie van meetdagen en meetwaarden de zelf gemeten bloeddruk het beste overeenkomt met de 24-uurs bloeddrukwaarde. Voor deze analyse werden alleen patiënten uit de zelfmeetgroep gebruikt. Om de invloed van patiënteneigenschappen op de bloeddrukhoogte te onderzoeken, werd de populatie verdeeld in leeftijdsgroepen, conventionele bloeddrukwaarden en geslacht. Zoals aangetoond in voorgaande studies blijkt de eerste zelf gemeten bloeddrukwaarde meestal hoger te zijn dan de daaropvolgende bloeddrukwaarden. Bovendien zijn de gemiddelde bloeddrukwaarden van de eerste dag altijd hoger dan van volgende dagen. De waarde die het best correleerde met de waarde van de

24-uurs bloeddrukmeting werd verkregen uit het gemiddelde van dag 3 tot en met dag 7, waarbij de eerste meting van iedere meet sessie werd weggelaten. Echter, de zelf gemeten bloeddrukwaarde van dag 3 tot en met dag 5 leverde gelijkwaardige resultaten op en is daarom ook aanvaardbaar. Patiënteneigenschappen bleken van invloed te kunnen zijn op de overeenkomst tussen zelf gemeten en 24-uurs bloeddrukwaarden. Zo was er een betere correlatie voor patiënten jonger dan 50 jaar dan voor ouderen en voor patiënten met lage dan met hoge conventionele bloeddrukwaarden. Verder bleek dat bij vrouwen een zelfmeting in de ochtend beter overeenkwam met de 24-uurs meting terwijl bij mannen de avondmeting juist beter bleek te correleren. De conclusie van dit onderzoek is dan ook dat, voor aanbevelingen met betrekking tot de zelfmeting van bloeddruk, rekening moet worden gehouden met patiënteigenschappen.

In hoofdstuk 6 hebben we geprobeerd om, met patiënten uit de zelfmeetgroep, de ware identiteit te achterhalen van een onlangs ontdekt fenomeen genaamd "gemaskeerde hypertensie". Dit is het verschijnsel dat patiënten een normale bloeddruk hebben tijdens de conventionele bloeddrukmeting terwijl uit het gemiddelde van de 24-uurs bloeddrukwaarden of zelf gemeten bloeddrukwaarden blijkt dat deze patiënten een verhoogde bloeddruk hebben. Het was tot nu toe onbekend of gemaskeerde hypertensie een soort aangeboren eigenschap van een patiënt is (en deze patiënten dus kunnen worden geclassificeerd als een specifieke groep) of gewoon het resultaat is van een uitzonderlijk verkregen meetwaarde. Volgens richtlijnen van de "European Society of Hypertension" zou gemaskeerde hypertensie gedefinieerd moeten worden als een conventionele bloeddrukwaarde lager dan 140 mmHg systolisch en 90 mmHg diastolisch terwijl zelf gemeten bloeddruk, of de dagwaarde van de 24-uurs bloeddrukmeting, gelijk is aan of groter is dan 135 mmHg en of 85 mmHg diastolisch. Bezwaarlijk aan deze definitie is echter dat hiermee alleen patiënten met bloeddrukwaarden rondom de bovengrens van deze definitie worden geclassificeerd en het voorbij gaat aan het feit dat ook patiënten met hogere bloeddrukwaarden een gemaskeerde hogere bloeddruk kunnen hebben. Bijvoorbeeld, als een patiënt tijdens de conventionele meting een bloeddruk heeft van 150/90 mmHg terwijl de gemiddelde dagwaarde 180/95 mmHg is, zal deze in beide gevallen als hypertensief geclassificeerd worden. Echter, deze patiënt moet agressiever behandeld worden op basis van de gemiddelde dagwaarde dan op basis van de conventionele bloeddrukwaarde gedaan zou zijn. Onderzoek heeft aangetoond dat het van klinisch belang is om dit effect ook te ontdekken bij patiënten met hogere bloeddrukwaarden. Om deze reden hebben we gebruik gemaakt van twee andere definities: 1) de zelf gemeten bloeddrukwaarde is tenminste 5 mmHg systolisch en 3 mmHg diastolisch hoger dan de conventionele bloeddrukwaarde: "de 5/3 definitie" en 2) de zelf gemeten bloeddrukwaarde is tenminste 10 mmHg systolisch en 6 mmHg diastolisch

hoger dan de conventionele bloeddrukwaarde: “de 10/6 definitie”. Resultaten laten zien dat, tijdens acht bloeddrukmetingen, 40% van alle patiënten tenminste één keer geclassificeerd is als gemaskeerd hypertensief op basis van de 5/3 definitie. Deze gemaskeerde hypertensie werd meestal veroorzaakt door een uitzonderlijk lage conventionele bloeddrukwaarde. Dit terwijl een classificatie als gemaskeerd hypertensief meestal resulteerde in toename van medicatie. Immers, patiënten werden behandeld op basis van hun (verhoogde) zelfmeting. Deze behandeling zou tevens ook de oorzaak kunnen zijn van de beperkte hoeveelheid patiënten dat bij herhaling gemaskeerd hypertensief was. Volgens de 5/3 en 10/6 definitie was het aantal gemaskeerd hypertensieven per meetmoment nagenoeg constant. Dit impliceert dat het effect dat leidt tot gemaskeerde hypertensie onafhankelijk is van de hoeveelheid medicatie en hoogte van de bloeddruk. De resultaten van dit onderzoek duiden erop dat gemaskeerde hypertensie geen erkenning verdient als eigenschap maar doorgaans het resultaat is van een uitzonderlijk lage conventionele bloeddrukwaarde. Om gemaskeerde hypertensie uit te sluiten verdient het dan ook aanbeveling om zelfmeting van bloeddruk te gebruiken naast de conventionele meting. Indien het niet mogelijk is om zelfmeting te gebruiken, zou een adequate bloeddrukbehandeling gebaseerd moeten worden op tenminste drie conventionele metingen tijdens drie verschillende visites.

Hoofdstuk 7 beschrijft de huidige kennis van gemaskeerde hypertensie. Het laat zien dat studies naar gemaskeerde hypertensie erg verschillen in type patiënten en toegepaste methoden. Hierdoor is het moeilijk om verschillende studies met elkaar te vergelijken en zo een goed beeld van dit fenomeen te krijgen. Echter, omdat gemaskeerde hypertensie sterk geassocieerd blijkt te zijn met orgaanschade is meer kennis over dit fenomeen van groot klinisch belang. Dit artikel pleit dan ook voor het opstellen van richtlijnen voor het onderzoeken van gemaskeerde hypertensie.

In hoofdstuk 8 is de reproduceerbaarheid van het fenomeen tegengesteld aan gemaskeerde hypertensie beschreven, namelijk dat van de witte jassen hypertensie. Voor deze analyse werden alleen patiënten uit de zelfmeetgroep gebruikt. Na acht meetperiodes liet 75% van de patiënten tenminste éénmaal een substantieel witte jassen effect zien. Een substantieel witte jassen effect was gedefinieerd als een conventionele bloeddrukwaarde die tenminste 20 mmHg systolisch en/of 10 mmHg diastolisch hoger was dan de zelfmeetwaarde of het daggemiddelde van de 24-uurs bloeddruk. Meer dan de helft van alle patiënten had tenminste één maal witte jassen hypertensie (een conventionele bloeddrukwaarde die gelijk is aan of groter is dan 140 mmHg systolisch en/of 90 mmHg diastolisch en een zelfmeetwaarde die lager is dan 135/85 mmHg). Na drie bloeddrukmetingen bleek 33% van de patiënten bij herhaling een substantieel witte jassen effect te hebben en 14% bij herhaling witte jassen hypertensief te zijn. Dit betekent voor deze patiënten dat zelfs bij

meerdere conventionele bloeddrukmetingen het witte jassen effect of witte jassen hypertensie niet ontdekt zou worden. Deze bevinding, samen met eerdere bevindingen over gemaskeerde hypertensie pleit dan ook voor invoering van zelfmeting van de bloeddruk in de reguliere gezondheidszorg. Immers, herhaaldelijk zelfmeten van bloeddruk zal voorkomen dat patiënten verkeerd beoordeeld worden als gevolg van het witte jassen effect of gemaskeerde hypertensie.

Hoofdstuk 9 is een literatuurstudie van alle onderzoeken naar zelfmeting van bloeddruk met als doel antwoord te krijgen op de volgende vragen: 1) hoeveel metingen zijn nodig voor een betrouwbare schatting van de werkelijke bloeddruk van een patiënt? 2) Wat zijn de normaalwaarden als het gaat om zelfmeting van bloeddruk? 3) In welke mate beïnvloedt zelfmeting van bloeddruk de medicatie? 4) In welke mate is zelfmeting van bloeddruk bepalend voor een prognose? Om goede antwoorden te krijgen op deze vragen moest de gebruikte literatuur (vanaf 1992) aan enkele eisen voldoen: 1) voor de zelfmeting van bloeddruk werd een gevalideerd apparaat gebruikt, 2) de zelfmeet procedure was voldoende duidelijk beschreven, 3) het was duidelijk hoe de verkregen bloeddrukwaarden berekend werden.

Na het samenvoegen van data uit de geselecteerde literatuur bleek dat voor een betrouwbare zelf gemeten bloeddrukwaarde tenminste twee dubbele bloeddrukmetingen per dag (twee 's morgens en twee 's avonds), voor drie dagen achtereen, nodig zijn. Omdat de gemeten bloeddrukwaarden van de eerste dag meestal hoger zijn dan van volgende dagen moeten deze weggelaten worden voor berekening van het gemiddelde. In navolging van aanbevelingen van de "European Society of Hypertension" en de "British Hypertension Society" bevestigen onze bevindingen dat de grenswaarde van 135 mmHg systolisch en 85 mmHg diastolisch correct is. Verder bevestigt deze literatuurstudie dat zelfmeting van bloeddruk een betrouwbaar middel is om de efficiëntie van een geneesmiddel te bepalen. Bovendien is zelfmeting superieur aan conventionele bloeddrukmeting voor wat betreft het voorspellen van schade aan hart, nieren en hersenen. Daarnaast heeft deze studie aangetoond dat, in onbehandelde patiënten, het verschil tussen conventionele en zelf gemeten systolische bloeddruk groter is bij mannen dan bij vrouwen en bovendien stijgt met de hoogte van de bloeddruk en leeftijd. Additionele bevindingen waren:

zelfmeting van bloeddruk

- geeft geen witte jassen effect en kan (zodoende) patiënten met witte jassen effect/hypertensie identificeren.
- levert veel metingen onder gestandaardiseerde omstandigheden met weinig variatie tussen metingen en verhoogt als zodanig de betrouwbaarheid. Dit is vooral belangrijk bij twijfel over wel of geen hypertensie en wanneer het

essentieel is dat bloeddruk goed wordt bepaald, zoals bij patiënten met type 2 diabetes mellitus en bij ouderen.

- verhoogt de bewustwording van hypertensie en verhoogt mede daardoor de therapietrouw. Dit leidt mogelijk tot een afname in sterfgevallen en kosten.
- leidt tot een verhoogde kans op het bereiken van de nagestreefde bloeddrukwaarde.

Interpretatie van alle samengevoegde data heeft tot de volgende aanbevelingen geleid:

- Gevestigde richtlijnen voor zelfmeet procedures moeten nauwkeurig worden nageleefd.
- Patiënten moeten uitgebreid worden geïnstrueerd door een daarvoor opgeleide verpleegkundige.
- Metingen moeten te allen tijden worden verricht met apparaten die gevalideerd zijn door tenminste één van de volgende autoriteiten: AAMI, BHS en/of ESH.
- Bloeddrukmeters moeten worden voorzien van een geheugen om te voorkomen dat patiënten niet de juiste waarden doorgeven.
- Omdat handmatige bloeddrukmeters sterk onderhevig zijn aan meetfouten mogen deze niet worden gebruikt.

Ondanks alle voordelen van zelfmeting heeft het ook nadelen:

- Evenals met 24-uurs bloeddrukmeting is zelfmeting niet geschikt voor mensen met een armomtrek waarvoor geen geschikte manchet voorradig is.
- Omdat de meeste apparaten de oscillometrische techniek gebruiken kunnen patiënten met een onregelmatige hartslag of met extreem verstijfde vaten niet goed worden gemeten. Dit laatste geldt vooral voor ouderen en patiënten met diabetes mellitus.
- De 24-uurs bloeddrukmeting blijft superieur aan zelfmeting omdat dit niet door de patiënt kan worden beïnvloed en bovendien de nachtelijke bloeddruk en de stijging van de bloeddruk rondom het ontwaken kan weergeven.
- Zelfmeting van bloeddruk is niet voor iedereen geschikt omdat het voor sommige patiënten te moeilijk is.
- Zelfmeting van bloeddruk kan angst veroorzaken of ertoe leiden dat patiënten hun medicatie gaan veranderen op basis van de door hen gemeten waarden.

De bijdrage van dit proefschrift aan de zelfmeting van bloeddruk

Omdat de bloeddrukhoogte sterk varieert gedurende een normale werkdag is het van essentieel belang meerdere metingen uit te voeren. Dit om te voorkomen dat er een verkeerde diagnose wordt gesteld, zoals geïllustreerd in dit proefschrift aan de hand van gemaskeerde en witte jassen hypertensie. Wanneer de bloeddrukwaarde over meerdere meetperiodes wordt bepaald blijkt het aantal patiënten met gemaskeerde hypertensie erg weinig voor te komen. Hierdoor kan gemaskeerde hypertensie veelal worden onthuld door tijdens meerdere visites de bloeddruk te meten. Indien het niet mogelijk is patiënten meerdere malen in de huisartsenpraktijk of kliniek te meten zal men, om dit fenomeen te onthullen, gebruik moeten maken van zelfmeting van de bloeddruk. Het witte jassen effect en witte jassen hypertensie zal bij een aanzienlijk deel van de patiënten niet verdwijnen na meerdere conventionele bloeddrukmetingen waardoor zelfmeting gewenst is om deze fenomenen te onthullen.

Voor een betrouwbare schatting van de bloeddruk moet, tenminste drie dagen lang de bloeddruk worden gemeten. Iedere dag moet bestaan uit twee ochtend- en avondmetingen. De gemiddelde waarde moet worden berekend uit dag 2 en dag 3. Echter, voor een optimale weergave van de dagelijkse bloeddruk zal vijf dagen moeten worden gemeten. Iedere dag moeten twee meetsessies worden gedaan (ochtend en avond) die bestaan uit drie metingen. Het gemiddelde moet dan worden berekend uit de metingen van dag 3 tot en met dag 5, waarbij voor iedere meet sessie de eerste meting wordt weggelaten. Wanneer patiënten ouder zijn, is het raadzaam om vaker de bloeddruk te meten.

Antihypertensie-behandeling kan veilig worden gebaseerd op bloeddrukwaarden verkregen met behulp van zelfmeting. Het zal leiden tot minder medicatiegebruik en daardoor tot kostenreductie voor de gezondheidszorg. Omdat ongeveer één miljoen mensen in Nederland, in meer of mindere mate, gebukt gaan onder hypertensie zal deze kostenbesparing een grote impact hebben op de maatschappij als geheel. Tenslotte, omdat automatische bloeddrukmeters in snel tempo verbeteren waardoor gemeten waarden betrouwbaarder worden en omdat zelfmeting van de bloeddruk kan leiden tot een lastenverlichting voor artsen verdient het aanbeveling om zelfmeting van bloeddruk te implementeren in de reguliere gezondheidszorg.

Dankwoord

Dankwoord

Dan is er nog het dankwoord, uit principe of bijgeloof (daar ben ik zelf nog niet helemaal uit) heb ik hiermee gewacht tot verder alles klaar was. Misschien niet zo handig want een dankwoord schrijven, zo is mij verzekerd, is nog moeilijker dan het schrijven van een artikel. Een dankwoord brengt namelijk het gevaar met zich mee dat er, met de finish in zicht, namen worden vergeten wat leidt tot boze, of nog veel erger, teleurgestelde lieden. Natuurlijk ben ik mij er ook van bewust dat het dankwoord veelal het verschil zal maken tussen het gelezen dan wel ongelezen in de “oud-papierbak” belanden van dit boekje. Ik zal er dus wel degelijk mijn best op doen.

Homerus' Odyssee wordt omschreven als “een zeer lange, vaak kwellende taak met grote uitdagingen, waarbij veel ervaring wordt opgedaan”. Ik had het zelf nooit zo doeltreffend en allesomvattend kunnen formuleren. Natuurlijk heb ik deze taak niet alleen volbracht, velen hebben mij op verschillende manieren bijgestaan en ben ik dank verschuldigd.

In de eerste plaats natuurlijk de vele patiënten die deelnamen aan het onderzoek want zonder hen zou ik niet eens aan dit dankwoord hoeven te beginnen. Daarmee heb ik het meest efficiënte deel van dit dankwoord gehad want verder wil ik iedereen afzonderlijk benoemen.

Mijn promotor Prof. dr. P.W. de Leeuw: Beste Peter, ik heb veel van je geleerd en jouw wetenschappelijke kennis heeft mij keer op keer verder geholpen en gezorgd dat ik enthousiast bleef, wat absoluut noodzakelijk was om dit proefschrift tot een goed einde te brengen. Ik vond het erg leuk ook jouw niet-wetenschappelijk kant te leren kennen zoals tijdens de schrijfweken in Frankrijk waar ik met veel plezier heb geluisterd naar talloze anekdotes uit van Kooten en de Bie's “keek op de week” en naar de heroïsche verhalen van de drie grootste bands uit de jaren 60: the Stones, the Beatles en the Stinging Needles.

Mijn co-promotor dr. A.A. Kroon: Beste Bram, jij was verantwoordelijk voor veruit de meeste HOMERUS-patiënten. Ook op niet afgesproken tijden kon veelal een beroep op jou worden gedaan als dit nodig was. Daarnaast heb je me de ruimte en vrijheid gegeven om zelfstandig aan dit project te werken wat heeft geleid tot grote uitdagingen en een rijke ervaring.

Prof. dr. Th. Thien: Beste Theo, jij was de meest kritische lezer van al mijn artikelen. Zelfs wanneer je niet rechtsreeks bij een artikel betrokken was vroeg je het te mogen lezen om vervolgens belangeloos met nuttige aanwijzingen te komen. Jouw kennis over en enthousiasme voor bloeddrukmeting: “ik ben een

freak", werkte bijzonder aanstekelijk en heeft mijns inziens geleid tot mooie resultaten waarvoor ik je zeer dankbaar ben.

Drs. ir. A.G.H. Kessels: Beste Fons, als "politieagent van HOMERUS" heb jij toegezien op de correcte uitvoer van de studie en hebt daarbij niet nagelaten om, indien nodig, stevig in te grijpen. Daarnaast was jouw statistische kennis essentieel en jouw programmeerkwaliteit meer dan welkom. Jouw uitspraak "ik ben een natuurkundig ingenieur en die kan alles" ga ik niet bevestigen maar ik wil wel benadrukken dat je als duizendpoot onmisbaar was voor deze studie.

Dr. P-H. van der Kuy: Beste Hugo, als apotheker kwam je bij onze studie voor farmacologische zaken maar jouw bijdrage was meer dan dat. Met jouw directheid was je als een katalysator voor de studie. Volgens mij zou iedere klinische trial dan ook een "van der Kuy" moeten hebben.

Dan was er nog het "HOMERUS-dagelijkse-gang-van-zaken-team"

In de eerste plaats dank ik natuurlijk de onderzoeksverpleegkundigen die het patiëntenonderzoek op zich namen: Heidi, Claudia Beyrus en Suuske. Niet alleen ik was blij met jullie werkzaamheden getuige de vele chocolade, de kaarten met kerst en natuurlijk de tranen als een patiënt de zo gevreesde afsluitende visite moest ondergaan. Heidi, een speciaal woord van dank aan jou: je bent de afgelopen jaren een enorme steun geweest, vooral toen we na een "succesvolle advertentie" de enorme inclusie bijna niet konden verwerken. Ik ben ervan overtuigd dat de ervaring die je hebt opgedaan een bruikbare bagage zal zijn voor je volgende uitdaging: promoveren op HOMERUS II. Bedankt dat je mijn paranimf wilt zijn.

Roger, ook jou wil ik zeker vermelden want jij hebt vele uren aan HOMERUS besteed en dat (ogenschijnlijk) nooit een probleem gevonden, jouw flexibiliteit en vriendelijkheid maakte dat jij altijd voor advies geraadpleegd kon worden, waarvoor hartelijk dank.

De overige Maastrichtse Homerianen: Jan, Patty, Carmen, Manuela, Daniëlle en Margriet dank ik voor de samenwerking en hun inbreng tijdens de vergaderingen.

Natuurlijk bedank ik ook de onderzoeksverpleegkundigen van de overige centra: Aarnout, Eugenie, Marianne en Annet. Ondanks de grote afstanden tussen de verschillende ziekenhuizen was de lijn altijd erg kort. Jullie communicatieve vaardigheden en precisie zorgden voor weinig misverstanden en bovenal voor een prettige samenwerking.

Beste Stella het invoeren van de ongelooflijke hoeveelheid HOMERUS-data heb jij voor je rekening genomen. Wat begon met een dagtaak werd al snel een bijna weektaak maar daar heb jij nooit een probleem van gemaakt. Door jouw precisie had ik soms het idee dat ik slordig ben (belachelijk toch!) wat jouw waarde voor deze studie onderstreept. Met jouw opgewektheid en dropot was je bovendien de perfecte kamergenoot.

De internisten die deel uitmaakten van het organisatiecomité van HOMERUS en bovendien verantwoordelijk waren voor de patiënten: Prof. dr. J.L. Lenders, Prof. dr. Th. Thien, dr. G.A. van Montfrans, dr A.J. Smit en dr. F.W. Beltman. Met HOMERUS hebben jullie het bewijs geleverd hoe goed de samenwerking tussen de verschillende academische ziekenhuizen kan zijn. Hopelijk is HOMERUS een voorbeeld voor en een aanzet tot meerdere toekomstige samenwerkingsprojecten.

Prof. dr. D.E. Grobbee dank ik voor zijn voorzitterschap van de "data monitoring committee" en adviserende rol.

De huisartsen Bakx, van de Broek, Castermans, Drost, Guldemon, de Grauw, van den Hoogen, Hoogervorst, Macco, Metz, Ubachs, Verhoeff en Voorhoeve dank ik voor hun inzet om patiënten te benaderen voor deelname en/of gedurende een jaar te vervolgen.

Zij werden gecoördineerd vanuit het "Regionaal Netwerk Huisartsenpraktijken" Maastricht onder leiding van Prof. dr. J.F.M. Metsemakers en het "Netwerk Academische Huisartsenpraktijken" Nijmegen dat werd aangestuurd door dr. C.J. Bakx en W.H.E.M van Gerwen.

Dan waren er nog de dames van de apothekers vereniging Maastricht die beter dan wie ook de weg wisten in de apothekerswereld en ervoor zorgden dat de apothekers de originele recepten ontvingen: Mariet, Olga en Denise bedankt voor jullie bijdrage.

Mijn directe collega's van het circulatielab dank ik voor de prettige samenwerking, niet onbelangrijk als je elkaar bijna iedere dag ziet: Claudia de Haan, Boy, Marieke, Esther, Kim, Marian, Ingrid, Monique, Dorien, Thomas, Jörgen, Melanie, Daniëlle, Peggy, Jolanda en, hoewel geen circulant, ook kamergenoot Dan. Last but not least: (nee ik vergeet je niet) Léon, bedankt voor de fijne samenwerking, de vele discussies en dat je mijn paranymf wilt zijn. Ik hoop dat we in de toekomst nog vaak samen kunnen werken.

Tiny, zoals bij velen ben je op het laatst ook voor mijn boekje een belangrijke rol gaan spelen. Zonder jou zou ik echt niet weten hoe ik mijn boekje zou moeten aanleveren, ik zie niet eens het verschil tussen de lettertypes "Arial" en "Blackadder ITC". Jouw inzet voor mijn boekje vond ik echt indrukwekkend en met jouw woorden: "bij ieder boekje ga ik te werk alsof het mijn eigen boekje is", heb je niets te veel gezegd. Ontzettend bedankt.

De leden van mijn beoordelingscommissie uit Maastricht Prof. dr. C.P. van Schayck (voorzitter), Prof. dr. J.W. van Ree, Prof. dr. J.L. Severens wil ik bedanken voor het kritisch beoordelen van mijn manuscript. Prof. dr. J.A. Staessen dank ik in het bijzonder; als inspirator voor HOMERUS hebt u een fundament gelegd voor dit proefschrift. Ik ben vereerd met uw plaats in mijn beoordelingscommissie. Prof. dr. G.S. Stergiou, I want to thank you for your willingness to review my manuscript. You being part in the jury is an honour as your work often served as a manual for my thesis. And off course there has to be a Greek involved in HOMERUS.

Dan zijn er nog personen die ik moet bedanken dat verder gaat dan alleen dit boekje. Mijn ouders: pap/mam jullie hebben het grootste deel van de weg hier naar toe vrijgemaakt. Jullie hebben mij geleerd dat de grootste beperking meestal door jezelf wordt opgelegd en dat er geen betere investering is dan in onderwijs. Altijd kon, en kan, ik op jullie terugvallen en daarom is jullie bijdrage aan dit proefschrift zo groot.

Tenslotte, de laatste die ik wil bedanken en tevens ook het moeilijkst omdat ik eigenlijk helemaal geen Homerus ben en dus de juiste woorden niet zal vinden. Anita, Je hebt me vaak gezegd het jammer te vinden dat je me niet kan helpen, waarmee je jezelf vreselijk onderschat. Niemand heeft me meer geholpen en gesteund dan jij. Of het nou mee of tegen zat jij was er altijd en zodoende ben jij het meest van iedereen bij dit proefschrift betrokken. Sterker nog, zonder jouw nuchtere kijk en humor had ik nooit het relativeringsvermogen en de energie gehad om dit project tot een goed einde te brengen. Sinds kort zijn we getrouwd en ik kan je niet zeggen hoe blij ik daarmee ben.

Curriculum vitae

Curriculum vitae

Willem Verberk werd op 20 mei 1975 geboren in Nijmegen maar groeide op in Wehl in de achterhoek. In 1994 behaalde hij het VWO diploma aan het St Ludger College in Doetinchem. In 1995 werd het staatsexamen Natuur- en Scheikunde behaald. Na één jaar geneeskunde te hebben gestudeerd aan het Rijks Universitair Centrum Antwerpen begon hij in 1996 aan de studie Medische Biologie aan de Vrije Universiteit van Amsterdam, waar hij in 2001 zijn bul behaalde. Datzelfde jaar ook begon hij met zijn promotieonderzoek onder leiding van Prof. dr. P.W. de Leeuw en dr. A.A. Kroon. Hij is getrouwd met Anita.