Blood Pressure Measurement in Cardiovascular Risk Stratification

Procedure, Progress, Process

A. Adiyaman
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Cover:

The cover shows a picture which consists of three parts. It resembles the last three words of the title of the thesis (procedure, progress, process).

In the upper part of the figure, the doctor measures the blood pressure of a patient. The procedure of measurement is essential for the determination of correct pressures and subsequently making adequate cardiovascular risk estimations. The middle part of the figure shows 24-hour trends of blood pressure in ambulatory monitoring. This technique is an important progress, because it measures pressures over the whole day and unmasks white coat hypertension and masked (hidden) hypertension. Additionally it provides the ratio of daytime and nighttime blood pressure, which is a marker of cardiovascular risk. The lower part of the figure depicts the process of indexes derived from blood pressure. The form of the blood pressure curve and the dynamic relation between diastolic and systolic pressure over 24 hours, establish indexes of arterial stiffness and cardiovascular risk. In the background of the cover page a watermark visualises the thorax of a patient, in which the heart and large arteries can be seen.
Blood Pressure Measurement in Cardiovascular Risk Stratification

Procedure, Progress, Process

Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift
ter verkrijging van de graad doctor
aan de Radboud Universiteit Nijmegen
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in het openbaar te verdedigen op dinsdag
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Ahmet Adiyaman
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The research presented in this thesis was carried out at the Dept of Medicine, Division of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

and

the Studies Coordinating Centre, Division of Hypertension and Cardiovascular Research, Department of Cardiovascular Diseases, University of Leuven, Belgium.

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I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.

If I keep this oath faithfully, may I enjoy my life and practice my art, respected by all men and in all times; but if I swerve from it or violate it, may the reverse be my lot.

Parts of the original oath of Hippocrates of Kos (460 BC – 370 BC), who separated the discipline of medicine from mystics and divine forces.

Voor mijn ouders
Voor de wetenschap
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Chapter 1

Introduction and aim of the thesis
Introduction

Atherosclerosis, with hypertension as its principal cause, is nowadays the most important risk factor for cardiovascular events (myocardial infarction, stroke, heart failure) and death[1]. The world is witnessing a remarkable demographical transition characterised by falling birth rates, lower mortality and increased longevity. In Europe, the proportion of inhabitants older than 60 years will rise from 20% now to over 35% by the year 2030. This unprecedented demographic revolution explains why the incidence of chronic age-related diseases, such as atherosclerosis and heart failure, will grow into larger proportions. These cardiovascular disorders will affect the quality of life of millions of Europeans. They will undermine the viability of the economical structure in Europe, unless appropriate preventive measures are implemented and therapies that are more efficacious become generally available[2].

Hypertension is an established and well known risk factor both for cerebrovascular and cardiac disease[1]. It is thought that, over a large range of blood pressures, there is a linear rise of cardiovascular risk, both for higher systolic and diastolic pressures[3]. Both antihypertensive medication and non-pharmaceutical methods to reduce blood pressure have effectively been shown to reduce cardiovascular disease and mortality[4]. This accounts both for isolated systolic and systolic/diastolic hypertension, from younger to very elderly patients[5, 6].

Blood pressure measurement; the procedure

Traditionally, blood pressure is measured by the physician at the brachial artery inflating and deflating an air-filled cuff. The first and fifth (last phase of) Korotkoff sounds indicate the border of no flow and the point of unimpeded flow through the artery, respectively reflecting systolic and diastolic blood pressure [7]. The biological variability of blood pressure is quite high, and many factors influence blood pressure itself or the blood pressure measurement[8].Therefore the procedure is highly standardized nowadays. Factors that influence blood pressure for example are physical activity, talking, a distended urinary bladder, environmental noises, the presence of a doctor, coffee consumption and time of meals. One of the factors that influence the blood pressure reading itself is the position of the patient (body position: upright, sitting or supine, leg position, arm position)[9]. With brachial blood pressure measurement, one wants to reflect the blood pressure present in the central aorta. Theoretically, because of differences in altitude between the central aorta and brachial artery, and because of the effect of gravity on the column of mercury, arm positions could influence the blood pressure reading. The exact influence of different arm positions on blood pressure readings in the sitting position has not been investigated in a proper way before. Furthermore, no studies were done to investigate the influence of different positions of crossing the legs, which is commonly done by patients in practice.
Blood pressure measurement; progress

Differences in the office versus at home.

With the introduction of home blood pressure measurement, it has been objectified that differences can be present between office and home blood pressure. Home blood pressure can be significantly lower than in the office and conversely can be significantly higher than in the office[10, 11]. The clinical significance of isolated office or “white coat” hypertension (WCH), a condition in which blood pressure is elevated in the clinic environment but normal in daily life, is still controversial. Some studies have shown the prevalence and degree of organ damage in subjects with WCH to be similar to that of normotensives[12, 13], whereas others have shown them to be greater than those of normotensives or even similar to that of hypertensive individuals[14, 15]. Furthermore longitudinal studies have not found this condition to be associated with an adverse cardiovascular prognosis. These studies sometimes had the limitation of a small number of cardiovascular events or a relatively short duration of the follow-up after WCH identification[16, 17]. Surprisingly, “masked” hypertension (MH), a condition in which BP is normal in the clinic environment but elevated in daily life, seems to have a similar prevalence in the population (10-20%)[11]. For MH however, in which hypertension is hidden from the doctor and therefore not adequately treated, there is consistent evidence that the cardiovascular risk is higher than in normotensives, and almost as high as in hypertensives[18, 19]. Both for WCH and for MH, it is not yet known how much the hospital environment and the presence of the doctor contribute to the blood pressure differences between home and the office.

Self blood pressure measurement.

With the introduction of automated measurement devices, self-measured blood pressure at home is being increasingly used[7]. It has proven to have a better reproducibility than conventional measurement, because of multiple measurements at home during the day[20]. Moreover, it provides more accurate estimates of the daily blood pressure, and hereby a better prediction of cardiovascular disease[21]. Because of the different place and setting of the blood pressure measurement in the office versus at home, and because of different techniques used (oscillometric in self blood pressure measurement versus auscultatory in conventional), differences in cut-off values for hypertension exist[22]. At present, results of 30 years of research regarding cut-off limits for hypertension and normotension of the self-measured blood pressure are available. Still, different guidelines report different cut-off values[22-24]. There is a need to comprehensively review all present literature, for various population groups, to define threshold levels for the diagnosis of normotension and hypertension, in order to choose subsequent treatment strategies.

Ambulatory blood pressure monitoring

Clinic (office) blood pressure measurement has been the basis for the established relationship between elevated blood pressure and cardiovascular morbidity and mortality[25]. Clinic blood pressure, however, may not necessarily represent an individual’s usual BP level and physicians frequently misclassify patients’ blood pressure status at the office when compared with ambulatory blood pressure monitoring (ABPM)[18]. ABPM helps to make therapeutic decisions in patients who exhibit discordance between clinic and ABPM values (WCH, resistant hypertension and MH)[26].
ABPM additionally has aided our understanding of BP circadian rhythm (24-hour period and night-day patterns) and has become an efficacious instrument helping to make therapeutic decisions in hypertensive patients and other subjects at risk of cardiovascular disease[27, 28]. Moreover, ABPM is more strongly correlated with target-organ damage than office BP and offers more accurate prognostic information of cardiovascular outcomes than office readings[14]. This has been clearly demonstrated in population-based surveys and both in treated and untreated hypertensive subjects[29]. In addition to the mean 24-hour BP level, variation in the day-night difference in BP (the dipping status) has also been claimed as an important predictor of both target-organ damage and cardiovascular events[30]. On average each 5% attenuation in the decline in nocturnal systolic/diastolic BP conferred approximately a 20% rise in the risk of cardiovascular mortality. Subjects with less than 10% BP decrease at night, or even an increase in BP during the night were those who exhibit a worse cardiovascular prognosis[27, 31, 32]. It has been claimed however that categorization of patients into dippers and nondippers is poorly reproducible[33]. Historically not only an attenuated nocturnal BP decline, but also a high nocturnal blood pressure itself was considered to be a determinant of an unfavourable prognosis[34]. In longitudinal studies and in meta-analyses, nocturnal BP seems to correlate better with signs of target organ damage and cardiovascular morbidity than daytime BP[34, 35]. Nondipping and high nighttime BP seem to share common determinants such as sympathetic overactivity, sleep apnoea, pressure-dependent natriuresis and underlying organ damage. Whether or not day and night blood pressures and their derived parameters can be targeted separately (chronotherapy), is a matter of ongoing debate[36].

Blood pressure measurement; process

Arterial stiffness and ambulatory blood pressure measurement

Because of ageing and atherosclerosis, normal healthy compliant arteries become stiff[37]. This process affects the properties of the walls of large arteries. This eventually results in plaque formation and ischaemic events (heart attack, stroke etc.)[38-41]. Until today traditional risk factors (the conventional office blood pressure, smoking, cholesterol etc.) are used for risk estimations. New methods are increasingly being implemented in the stratification of cardiovascular risk and show a better performance than the classical risk factors. Examples of such methods are intima media thickness (highly standardized measurement of arterial vessel wall thickness by ultrasonography)[42], coronary calcium score (CT indexed evaluation of calcium deposits in the coronary vasculature), and indexes of arterial stiffness, like pulse wave velocity (measurement of blood flow velocity over the large arteries by special equipment)[43] and the newest of them all: the ambulatory arterial stiffness index (AASI)[44].

Cardiologists in The Netherlands generally practice active cardiology, both during and in the aftermath of a cardiovascular event. In this regard the adage ‘better to prevent than to cure’ is relatively being overlooked in the Netherlands. Preventive cardiology is practiced by the general practitioner (GP) and to a lesser (but more refined) extent by the vascular internist. Especially for the GP, but also for internists and cardiologists, easy to handle measures are needed for diagnostic and therapeutic decision making. All above mentioned new indexes have proven to predict cardiovascular disease above and beyond the traditional risk factors[39, 41, 45, 46], however only AASI does not require special equipment and highly trained technicians, since it can be derived from simple 24-hour ABPM.

In 1914, MacWilliam and Melvin wrote that loss of elasticity in the arterial system influences the height of the diastolic BP and its relation to systolic BP[47]. Within an international group
of researchers, it was hypothesized that the slope of diastolic BP on systolic BP during ambulatory monitoring might be a measure of arterial stiffness[44]. From individual 24-hour recordings, the regression slope of diastolic BP on systolic BP was computed. AASI was defined as 1 minus the regression slope (figure 1). The slope was not forced through the origin, because when blood inflow from the ventricle stops during diastole, BP does not fall to zero, as a new ventricular contraction takes place. With the AASI, one can search to distinguish between low risk and high risk patients, beyond BP and pulse pressure (see figure 2). There are already very promising results in terms of prediction of cardiovascular events and mortality[40, 41, 46, 48]. Before implementing this new risk-stratifying tool at large scale, the new technique should be validated. One way to do this is to comprehensively review the literature. Furthermore the determinants of the AASI should be further explored and the reproducibility of this new index should be determined.

**Figure 1.** Derivation of the ambulatory arterial stiffness index from a 24-h ambulatory blood pressure recording in one participant, whose 24-h BP was 129 mmHg for systolic blood pressure and 95 mmHg for diastolic BP.

**Figure 2.** Plots of diastolic blood pressure regressed on systolic blood pressure in 4 different subjects. For comparable levels of 24-h blood pressure and pulse pressure, ambulatory arterial stiffness index varied from 0.33 to 0.56. From left to right, the calculated mean blood pressure was 89, 98, 122 and 117 mmHg.
**Aim of the thesis**

The aim of the first part of this thesis was to study the effect of different arm positions on the results of the BP measurement and of different leg positions on the BP. Firstly, in mainly treated hypertensives, we studied the differences of BP when the arm was positioned at chair support level or at desk level in the sitting position, compared to the BP measured with the arm at heart level. Secondly, we studied in hypertensives, diabetics and normotensives if crossing the legs at the level of the knee and at the level of the ankle, had an influence on BP. Finally we studied the physiological principle of BP changes initiated by crossing of the legs at the level of the knee.

In the second part of this thesis, we studied BP differences between the home setting and hospital settings, with and without the presence of a doctor. From that we calculated the separate contributions of the presence of a doctor and the hospital environment itself. Further, we searched for defining thresholds for normotension and hypertension for the self measured BP at home. We comprehensively reviewed 30 years of literature to determine thresholds for the self measured BP at home, in order to determine levels of cardiovascular risk. We reviewed two meta-analyses, several prospective outcome studies in populations and in hypertensive patients, studies in pregnant women, three clinical trials, and the thresholds proposed in previous and current hypertension guidelines. With this review, we have tried to provide an insight into the present literature in order to choose optimal treatment strategies.

In the last part of the thesis we focused on the newest evolution of 24-h ABPM, namely the AASI, a new non-invasive marker of arterial stiffening, and thereby of cardiovascular risk. We reviewed the already large number of studies reported after 2006, and provided a comparison with the gold standard of non-invasive determination of arterial stiffness, the pulse wave velocity. Furthermore, we studied the short-term reproducibility of the new index, which is essential for the implementation of the AASI into daily clinical practice. We included a few communications and analyses, which is only part of the vast amount of debate generated by this new index. Finally we investigated whether the goodness of fit of the AASI regression line (see figure 3) could possibly be a marker of the quality of the AASI measurement, and whether it enhances the power of AASI in reflecting arterial stiffness and cardiovascular disease.

**Figure 3.** Three patients with the same ambulatory arterial stiffness index (0.50), approximately the same number of blood pressure readings (49-56), however a different goodness of fit of the regression line ($r^2$ of 0.23 up to 0.86) determining the ambulatory arterial stiffness index. The less scatter around the fitline, the higher the goodness of fit (right).
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Part 1

Aspects of the procedure of blood pressure measurement

Chapter 2.1

The position of the arm during blood pressure measurement in sitting position.

Ahmet Adiyaman
Rutger Verhoeff
Jacques W.M. Lenders
Jaap Deinum
Theo Thien

Abstract

Objective Determining the influence of the position of the arm on blood pressure measurement in the sitting position.

Methods Blood pressure of 128 individuals (the majority being treated hypertensive patients) visiting the outpatient clinic was measured simultaneously on both arms with arms in two different positions. First, both arms were placed at the chair support level and blood pressure was measured three times on both arms after 10 min of rest. Subsequently, while still remaining in the same sitting position, five blood pressure measurements were made simultaneously at both arms with one arm placed on the desk and one arm placed and supported at heart level (mid-sternal). The arm placed at heart level served as the reference arm. The choice of which arm was placed at desk level and which arm was placed at heart level was randomized.

Results Both at desk level and at chair support level, mean (± SD) systolic and diastolic blood pressures were higher than blood pressure at heart level by 6.1/5.7 ± 4.6/3.1 and 9.3/9.4 ± 5.4/3.4 mmHg, respectively. The effect of the height differences between the arm positions on the blood pressure readings was smaller than predicted (0.49mmHg/cm systolic and 0.47mmHg/cm diastolic). No significant correlation was found between blood pressure difference in the different arm positions (desk and heart level) and age, sex, weight or baseline blood pressure.

Conclusions Different arm positions below heart level have significant effects on blood pressure readings. The leading guidelines about arm position during blood pressure measurement are not in accordance with the arm position used in the Framingham study, the most frequently used study for risk estimations.
Introduction
Blood pressure (BP) measurement is considered an easy routine procedure, but carries many potential errors. Generally, few of the many factors that can affect the results of BP measurement are taken into account [1–3]. One of the often-neglected factors is the position of the arm and the body of the patient during BP measurement [4–6]. These might have substantial effects on BP readings.

In some guidelines, BP in sitting and supine positions is regarded as identical, sometimes with the addition that the arm must be positioned at heart level (right atrium or tricuspid valve) [7,8]. Earlier studies of our group [9,10] showed that body position has influence on BP, so this factor must be taken into account. Although previous research concluded that the arm position had a great influence on BP readings [11–20], in many studies the arm position is not sufficiently mentioned [5,21]. In daily practice, we commonly observe that the arm is placed on the desk, on the chair support or is even left hanging. BP is measured to give an estimation of the risk for long-term cardiovascular complications. One of the main studies in this field is the Framingham study [22]. In that study, the arm position during BP measurement was at desk level. According to the latest guidelines of the British Hypertension Society [23] and American Heart Association [24], BP must be measured with the upper arm (and center of the cuff) at heart level (mid-sternal). Although this is theoretically correct, it is at variance with the method of BP measurement in the Framingham study. If BP measured with the arm at desk level, as used in the Framingham study, differs from BP measured with the arm at heart level, as advised in the recent guidelines, the guidelines should be adjusted or the Framingham study should not be used for risk estimation. To our knowledge, the difference between BP measurement with the arm at heart level (guidelines) and the BP measurement according to the Framingham study has not been investigated earlier. Therefore, in the present study, we investigated the difference of BP readings, with the arm position at desk level and at chair support level, to compare these to the ‘gold standard’: BP measurement with the upper arm at heart level.

Study participants
Participants were patients visiting the outpatient clinic routinely (most of them were treated hypertensive patients) and medical students. The two exclusion criteria were cardiac arrhythmias and a left/right BP difference of more than 10mmHg.

Methods
First the whole investigational procedure was extensively explained to the patients, to prevent muscle exercise, talking, movements or emotions from inducing falsely high BP readings. The investigator started with a simultaneous BP measurement on both arms with a validated oscillometric BP measurement device (Omron CP 705; Omron Healthcare Inc., Bannockburn, Illinois, USA) [25] in order to exclude a significant left/right arm difference. We used different cuffs of 23 x 13 and 36 x 13 cm for upper arm circumferences of <30 and ≥30 cm, respectively. Subsequently, the patients were placed in a comfortable chair with the arms on the chair support. In the type of chair we used (Fig. 1), the back and the head were supported. We standardized the height of both the chair support and the desk, measuring 67.5 and 77 cm above the floor, respectively.

Before starting with BP measurements, a self-built stand was prepared to make sure the arm later used as reference value was precisely at heart level. This stand had an arm support that could easily be changed in height. The position of the stand and thus the centre of the cuff of the BP measurement device had to be at heart level (mid-sternal) as exactly as possible (Fig.
1). This was checked by using a water level. The arm support consisted of soft material in order to prevent irritation. The precise height differences between arm positions (at desk level or chair support) compared with heart level were measured.

**Fig. 1**

The set-up of measurements in different arm positions. On the left, the participant has both arms at chair support level. On the right, the participant has one arm at desk level and the other arm placed at heart level (with a specially developed support). Three lines are drawn on the T-shirt of the participant. The upper line reflects the jugular notch and the lower line the xiphoid process. Mid-sternal is defined as halfway between these two lines.

After these preparations, the investigator left the room for an acclimatization period of at least 10 min. Subsequently, the investigator re-entered and BP was measured simultaneously three times at both arms (2 x 3) with arms on the chair support. Then, the patients were asked to put one arm on the desk and the other on the self-built stand functioning as the control arm (at heart level). The choice of which arm was supported by the stand was randomized.

Consequently, 1–2 min after changing the arm positions, simultaneously five BP measurements were performed bilaterally, leading to average BP values for the arm at desk level and at heart level. All measurements were carried out in a quiet room with constant temperature by the same investigator (R.V.), who was instructed and trained before the study, in order to prevent factors influencing BP, such as talking, movements, etc.

**Statistical analysis**

The average of the three readings with the arm on the chair support was compared with the averages of the five readings with the same arm lying on the desk or the five readings at heart level (reference value). So, always the readings in the same arm were compared with each other. Simultaneous readings in different arms were only used in comparison between BP at heart level and BP at desk level. Mean differences of BP between arm positions were calculated with their SDs. The 95% confidence intervals were calculated to look for significance between all differences of BP (arm at heart level versus arm at desk level and arm at chair support level). We looked for the influence on BP of the absolute height difference from the heart (with arm both at desk level and at chair support level). The correlations between height, weight, age, baseline BP and difference of BP in different arm positions were investigated. All correlations were corrected for the other variables. Furthermore, the influence of sex on BP differences was analysed, after correction for length.
Results
When the first BP reading showed a left–right difference of more than 10mmHg, the further procedure was stopped. Owing to a left–right BP difference of more than 10mmHg (systolic or diastolic; mean of the three BP readings at chair support level), however, we had to exclude another four patients. Finally, 128 patients participated: 63 female and 65 male. Table 1 shows the clinical characteristics.

Table 1  Clinical characteristics

<table>
<thead>
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<tr>
<td>Number (male/female)</td>
<td>128 (65/63)</td>
</tr>
<tr>
<td>Age (mean ± SD) (years)</td>
<td>54 ± 15</td>
</tr>
<tr>
<td>Range (years)</td>
<td>21–79</td>
</tr>
<tr>
<td>Height (mean ± SD (cm))</td>
<td>170 ± 9</td>
</tr>
<tr>
<td>BMI (mean ± SD (kg/m²))</td>
<td>26.6 ± 3.5</td>
</tr>
</tbody>
</table>

BP values (mmHg) and HR (beats/min) with arms on chair support (mean ± SE)

| Left SBP/DBP              | 139/83 ± 2/1 |
| Left HR                   | 67 ± 1     |
| Right SBP/DBP             | 140/83 ± 2/1 |
| Right HR                  | 67 ± 1     |

BMI, body mass index; BP, blood pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

No significant left–right difference was present in the mean of the three readings with the arms on the chair support. When analysed individually, 64% of the systolic blood pressure (SBP) readings and 84% of the diastolic blood pressure (DBP) readings had a left–right difference of <4.0mmHg. Table 2 shows the average BP values of the sessions with both arms on the chair support, on the desk and at heart level (Fig. 1).

The BP at desk level was SBP/DBP 6.0/5.8mmHg higher than that at heart level. The difference was even larger when the BP with the arm on the chair support was compared with the BP with the arm at heart level; 9.3/9.4mmHg. The 95% confidence intervals (Table 2) show that the differences of BP between arm position on the chair support and arm position at desk level were both significant compared with the BP with the arm at heart level. The BP difference between the arm on the chair support and the arm on the desk was also highly significant. Eighty-nine percent of the study population had a higher SBP and DBP when the arm was at desk level and 95% of the study population had a higher SBP and DBP when the arm was at chair support level than the readings taken with the arm at heart level.

Table 2  Mean blood pressures and the differences of blood pressure with the arm in different positions

<table>
<thead>
<tr>
<th>Arm position</th>
<th>Sitting SBP/DBP (mean ± SE) (mmHg)</th>
<th>Difference vs. HL SBP/DBP (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart level (mid-sternal)</td>
<td>130/73 ± 2/1</td>
<td>6.0/5.8 [6.6–6.4/5.6–6.1]</td>
</tr>
<tr>
<td>Desk level (77 cm)</td>
<td>136/79 ± 2/1</td>
<td></td>
</tr>
<tr>
<td>Chair support level (67.5 cm), same arm as HL</td>
<td>139/83 ± 2/1</td>
<td>9.3/9.4 [8.4–10.3/8.8–10.0]</td>
</tr>
<tr>
<td>Chair support level (67.5 cm), same arm as desk</td>
<td>140/83 ± 2/1</td>
<td>9.5/9.5 [8.5–10.4/8.9–10.1]</td>
</tr>
</tbody>
</table>

CI, confidence interval; HL, heart level; SBP, systolic blood pressure; DBP, diastolic blood pressure.
No significant differences were present between men and women. Statistical analyses showed no correlation at all of BP differences with age, weight or baseline BP, after correction for each other. A weak correlation (SBP: r=0.17, P=0.04; DBP: r=0.16, P=0.06) was found between the height of the participant and the BP difference between arm positions, only for the BP difference between desk and heart level.

The mean absolute height difference between the arm at desk level and at heart level was 12.2 cm. The difference between heart level and chair support level amounted to an average of 21.7 cm. This means that, when compared with heart level, at desk level there was a mean difference (mean absolute height difference/mean BP difference) of 0.49/0.47mmHg/cm and at chair support level this was 0.43/0.43mmHg/cm.

Discussion
The present study shows that BP readings with the arm at chair support level and at desk level, as used in the Framingham study, differs significantly and relevantly from BP reading with the arm at heart level. The difference increases when the arm is placed at a lower level, and logically the difference at chair support level is larger than that at desk level.

In our study, the absolute height difference of the arm between desk and heart level varied from 6 to 23 cm, depending on the height of the participant. This resulted in substantial differences of BP readings. In theory, the physiology of this effect can be explained by gravity on the column of blood causing a 0.74mmHg rise of BP reading for each centimetre below heart level. In our study, we found a smaller rise per centimetre. Hypothetically, the minimal effort made when placing the arm from chair support level to heart and desk level could have increased the BP, thereby reducing the difference of BP reading found. Only a SBP decrease of 1.8 mmHg, however, was observed during the course of the five BP readings. We have no other plausible explanation for the discrepancy between theory and practice. This suggests that possibly other factors besides gravity play a role. If only gravity would play a role, one could adjust BP for the height difference from the mid-sternal level. The fact that such an adjustment is not possible underlines the importance of guidelines to advise measurement of BP with the upper arm at heart level.

In this study, we worked with a standardized height of chair support and desk. In our clinic, the desk heights varied from 75 to 77 cm, and the chair supports varied from 66 to 69 cm with the height of the sitting compartment varying from 45 to 48 cm. This resembles the situation in other clinics. Simple manoeuvres to reduce the deviation from BP at heart level could be adjusting the height of the chair when the arm is on the desk, or raising the chair support when the arm is on the chair support.

A weakness of our study is that heart level was determined subjectively by the investigator (although always with the same criterion, mid-sternal). An advantage of our study is the use of an automated validated device that circumvents observer bias. In addition, we had one trained investigator, multiple readings, standardized facilities and a large number of participants. We also compared both chair support level and desk level with heart level, which has not been done previously.

When we consider previous studies regarding the influence of arm positioning on BP performed with patients in a sitting position, we see that all studies support our findings (see Table 3 [11–20]). Generally, the influence on BP of placing the arm on the chair support or placing the arm hanging were compared with that of placing the arm at heart level. ‘Heart
level’, however, was not always precisely defined and/or determined. In a number of studies, details about essential aspects of BP measurement were not mentioned (Table 3). An incomplete reporting of the BP measurement method frequently occurs in the literature. A previous publication [3] shows that rather frequently important aspects of BP measurement are ignored by doctors and nurses. In general medical journals and even in specialized hypertension journals, important details about BP measurement are often not mentioned [1,2].

Table 3  Summary of previous research about differences in blood pressure readings in different arm positions, compared with arm at heart level, with the body in sitting position

<table>
<thead>
<tr>
<th>Author(s)/Reference</th>
<th>Year</th>
<th>Sample</th>
<th>Device for BP measurement</th>
<th>n</th>
<th>Difference of SBP/DBP (mmHg) compared with HL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn [11]</td>
<td>1919</td>
<td>27 Nt</td>
<td>Mercury</td>
<td>?</td>
<td>Vertical arm: +14/+13, 45° elevation of arm: +8/+6</td>
<td>Korotkoff IV was used for DBP; no information about rest period and number of observers; no information about number of BP-readings</td>
</tr>
<tr>
<td>Merendino and Finiti [12]</td>
<td>1991</td>
<td>78 Nt</td>
<td>26 Ht</td>
<td>Aneroid</td>
<td>?</td>
<td>With arm dependent: +11/+12</td>
</tr>
<tr>
<td>Krause and Klepzig [13]</td>
<td>1983</td>
<td>100 (mostly) men from clinic</td>
<td>Mercury</td>
<td>3</td>
<td>Arm at 3 levels: (i) 10 cm below HL: +10.0/+10.1; (ii) 4.5 cm above HL: +9.3/+9.5; (iii) 16.5 cm above HL: +12.4/+17.0</td>
<td>No information about number of observers</td>
</tr>
<tr>
<td>Mitchell et al. [14]</td>
<td>1994</td>
<td>139 Middle-aged men</td>
<td>Mercury</td>
<td>1</td>
<td>With arm on sternomastoid junction level: -5.0/-4.6, with arm on apleothoracic junction level: +6.0/+5.7</td>
<td>No information about number of observers</td>
</tr>
<tr>
<td>Webster et al. [15]</td>
<td>1984</td>
<td>90 Ht outpatients</td>
<td>Mercury</td>
<td>2</td>
<td>With arm dependent: +11/+12</td>
<td>Two observers</td>
</tr>
<tr>
<td>Toren and Breig-Ashberg [16]</td>
<td>1994</td>
<td>401 persons from healthy population</td>
<td>Mercury</td>
<td>3</td>
<td>With upper arm parallel to sternum and arm on a chair support ‘at examination table level’: +6.8/+12.9</td>
<td>–</td>
</tr>
<tr>
<td>Nette et al. [17]</td>
<td>1999</td>
<td>69 out-clinic patients, mostly treated Ht</td>
<td>Oscillometric and mercury</td>
<td>3</td>
<td>+9.7/+10.8 at chair support level with mercury and +7.3/+8.3 for automatic device</td>
<td>Oscillometric (left arm) and mercury (right arm) BP readings were simultaneously performed</td>
</tr>
<tr>
<td>Nette et al. [18]</td>
<td>2002</td>
<td>142 DM 1 and 2 out-clinic patients, mostly Ht</td>
<td>Oscillometric</td>
<td>3</td>
<td>Arm at support of chair: +6.2/+7.9</td>
<td>–</td>
</tr>
<tr>
<td>Mourad et al. [19]</td>
<td>2003</td>
<td>26 Ht and 25 Nt</td>
<td>Oscillometric and mercury</td>
<td>?</td>
<td>Arm dependent: +8/+7 Nt (mercury); +10/+10 Nt (oscillometric); +29/+10 Ht (mercury); +18/+9 Ht (oscillometric)</td>
<td>No information about number of BP-readings; oscillometric and mercury BP readings were performed after each other (randomized)</td>
</tr>
<tr>
<td>Hemingway et al. [20]</td>
<td>2004</td>
<td>100 various patients in hospital</td>
<td>Oscillometric</td>
<td>1</td>
<td>Arm dependent: +8.8/+10.1 vs. arm perpendicular to torso</td>
<td>More investigators (number unknown); no information about rest period is given; arm perpendicular to torso does not resemble HL</td>
</tr>
</tbody>
</table>

BP: blood pressure; n, number of BP readings per arm position; SBP, systolic blood pressure; DBP, diastolic blood pressure; HL, heart level; Nt, normotensive; Ht, hypertensive; DM, diabetes mellitus.

Some of the guidelines [23,24] advise one to measure BP with the arm supported at heart level (mid-sternal). As cardiovascular risk calculations are based on the Framingham study, however, it is important to realize that during the BP measurement in the Framingham study, the arm was not supported at heart level. In the Framingham study, BP was measured as follows: ‘The blood pressures were taken with the patient in sitting position, the left arm resting on the examiner’s desk.’ On the same page the authors state that BP is measured once by a nurse and twice by a doctor (one at the beginning of the physical examination and a second at completion). This is not an ideal situation and is certainly not comparable to the present BP measurement guidelines. Do we, however, really want to measure according to the reference BP? The main purpose of measuring BP is to give a good risk estimation of cardiovascular disease in the future. The guidelines and the studies with the best risk estimations must be in agreement with each other. After all, ‘true’ BP is not important, but the
prognostic value of the measured BP is. When BP is measured at heart level, it underestimates
the risk on morbidity and mortality, compared with measuring at desk level (like in the
Framingham study).

Therefore, arm positioning in the study with most reliable risk estimations should be
synchronized with the leading guidelines.

In conclusion, our findings indicate that important differences of BP reading in sitting
position can be present when measuring BP in different arm positions. The guidelines are not
in conformity with those of the Framingham study. More attention should be paid to the arm
position during BP measurement and to the description of the method/protocol used for BP
measurement in scientific journals.
References

12 Merendino J, Finnerty FA Jr. Importance of the position of the arm on the level of arterial blood pressure. JAMA 1961; 175:51–53.


Part 1

Aspects of the procedure of blood pressure measurement

Chapter 2.2

The effect of crossing legs on blood pressure.

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Lammy D. Elving
Jaap Deinum
Jacques W.M. Lenders
Theo Thien

Blood Press Monit 2007; 12(3):189-93
Abstract

Objective To determine whether crossing of the legs at the knee or at the ankles during blood pressure measurement in sitting position has an effect on blood pressure.

Methods One hundred and eleven patients, 60 women, mean age 52± 17 years (19–80): 49 chronically treated hypertensives, 28 treated diabetics and 34 normotensives were measured by one trained investigator, with an oscillometric device (Omron 705CP) on the left arm. We looked for the difference of blood pressure with the ankle or the knee crossed versus the uncrossed position.

Results Leg crossing at the knee during blood pressure measurement increased systolic blood pressure significantly by 6.7 (95% confidence interval 5.0–8.4) mmHg in the hypertensives and 7.9 (4.0–11.8) mmHg in the treated diabetics. Diastolic blood pressure increased by 2.3 (0.8–3.8) mmHg in the hypertensives and 1.7 (0.1–3.4) mmHg for the treated diabetics. Normotensive participants showed a smaller, though significant, increase of systolic blood pressure 2.7 (1.2–4.2) mmHg, but not significant for diastolic blood pressure, – 0.1 (– 1.5–1.3) mmHg, respectively. In all groups there was no effect of crossing the ankles on blood pressure. No differences were found between men and women. No significant correlation between the increase of the blood pressure when the knees were crossed and BMI, age or baseline blood pressure was present.

Conclusions Blood pressure increased when legs were crossed at the knee in the sitting position. No significant increase of blood pressure was found when crossing the legs at the ankles. Leg position during measurement of blood pressure should be standardized and mentioned in publications.
Introduction

Blood pressure (BP) measurement is one of the most commonly used techniques in the diagnosis and treatment of various medical problems. When hypertension is suspected, with its lifelong consequences for treatment, accurate measurement of BP is crucial. Therefore, all efforts should be made to eliminate errors in measuring BP.

Many physiological stimuli influence BP measurement, varying from talking during BP measurement to food intake before BP measurement [1]. Previously we have demonstrated that both body and arm position considerably influence BP [2]. Another potential effect on BP measurement in the sitting position is the effect of crossing the legs. Some guidelines on BP measurement (JNC VII, AHA, nursing guideline) contain recommendations on the position of the feet by advising to keep both feet on the floor [3–5], whereas other important guidelines (BHS and ESH) do not mention leg position [6,7].

In daily practice, BP is measured in a chair with the back supported. As it seems a comfortable position, we frequently see that patients spontaneously cross their legs at the knee, at the ankles, or even with the ankle over the knee.

In limited previous studies assessing the effect of crossing the legs on BP, only crossing the legs at the knee and ankle over knee was investigated [8–12]. These studies had some methodologic shortcomings and the results were not equivocal. The most unnoticed and most frequently used crossing of the legs, at the ankles, was not evaluated. For this reason we wanted to assess the effect on BP of crossing the legs at the ankles. Moreover, we wanted to reconfirm previous findings in other studies about the influence on BP of crossing the legs at the knee, using a meticulous methodology. Further we wanted to study the effects of crossing the legs in three different subgroups, respectively normotensives (Nt), treated hypertensives (Ht) and diabetics (DM).

Therefore, the aim of this study was to investigate the effects of crossing the legs at both the ankles and the knees in Nt, Ht and in patients with diabetes. Patients and methods

Sample

The study group comprised 111 patients: 49 treated Ht, 28 DM (diabetes mellitus type 1 or 2) and 34 Nt. Participants were excluded from this study if they had a history of peripheral vascular disease or surgery of lower extremities. Other exclusion criteria were renal failure (serum creatinine >150 mmol/l), cardiac rhythm disorders and an upper arm circumference above 33 cm (no bladder was available). Informed consent was obtained from all participants before their participation in the study. The local ethics committee approved the protocol.

Measurement of blood pressure

One investigator (N.T.) performed all BP measurements. The investigator was informed and trained immediately before the study to prevent factors influencing BP. BP measurements were done in the outpatient clinic in a quiet room, which was at a constant temperature. Patients were seated in a comfortable chair with stable back and arm support. To eliminate observer bias we measured BP using a validated, new purchased and fully automated Omron 705 CP oscillometric device (Omron Healthcare Europe B.V., Hoofddorp, The Netherlands)[13]. Arm circumference was measured and a bladder was used fitting arms 22.9 to 33 cm in circumference. All patients were previously instructed to take their normal BP medication on the day of the measurements.
Before taking a BP reading, the participant was seated and instructed to place his or her feet flat on the floor, to remove constricting clothing and to refrain from talking or moving the arms during the procedure[14]. A first reading (simultaneously with two automatic Omron’s at both arms, without a rest period) was done, to assess left to right arm BP difference. If this difference was >10mmHg, the patient was excluded. After this all patients rested seated for at least 8 min[15] with the feet flat on the floor (with the cuff in place). BP was measured at the left arm in all patients. After the rest period two measurements were performed in the baseline position (legs uncrossed with feet on the floor). Subsequently the legs were crossed at the ankle (lateral malleolus over the other lateral malleolus) or at the knee (popliteal fossa of one leg over the suprapatellar bursa of the other) (Fig. 1). This was done in a randomized order. After 4min in this position (to reach a steady state) BP was measured in triplicate. Then again the baseline position was taken and after 3 min of rest BP was measured twice. Subsequently the other crossing position was taken and again after 4 min the BP was measured three times. Finally, the baseline position was taken and the last two measurements were done after 3 min of rest. Statistical analyses The differences between the BP measurement in the crossed position and the resting position were calculated by subtracting the mean of the rest position (the mean of six readings in the three baseline positions with feet flat on the floor) from the mean of the BP measurements in the crossed two positions (average of three readings per position). Mean values of the crossed and uncrossed position were compared and 95% confidence intervals (CIs) are given. An evaluation was made how many participants had a systolic BP (SBP) rise of >5 and >10mmHg, and diastolic BP (DBP) rise of >5 and >10mmHg.

Fig. 1

On the left the crossing position at knee level is shown and on the right the crossing position at the ankles.

The correlation between the difference of BP between positions and the age, BMI and baseline BP in the groups was calculated using the Pearson correlation coefficient (r). The level of significance was set at a P-value <0.05 (two-sided). Age and BMI effect were also
examined in stratified groups (age <35, 35–60, >60 years and BMI <30, ≥30). Significance was stipulated by means of student t-test and 95% CIs.

Results
The clinical characteristics of the study population are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Ht</td>
</tr>
<tr>
<td>Number</td>
<td>49</td>
</tr>
<tr>
<td>Men</td>
<td>22</td>
</tr>
<tr>
<td>Age ± SD (range)</td>
<td>56 ± 12 (22–60)</td>
</tr>
<tr>
<td>BMI (kg/m²) ± SD (range)</td>
<td>27 ± 4 (20–35)</td>
</tr>
<tr>
<td>Mean height (cm)</td>
<td>174</td>
</tr>
</tbody>
</table>

Table 2 demonstrates the baseline BP values during the three periods with the feet flat on the floor and the mean of these three readings (three times two readings of left arm).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The mean of the SBP/DBP/HR of the three starting positions (three baselines, six readings) with their SD for the three different groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ht</td>
</tr>
<tr>
<td>SBP/DBP (mmHg) n=49</td>
<td>142/87 ± 31/17</td>
</tr>
<tr>
<td>Baseline 1</td>
<td></td>
</tr>
<tr>
<td>SBP/DBP (mmHg) n=28</td>
<td>138/85 ± 31/17</td>
</tr>
<tr>
<td>Baseline 2</td>
<td></td>
</tr>
<tr>
<td>SBP/DBP (mmHg) n=34</td>
<td>139/85 ± 30/17</td>
</tr>
<tr>
<td>Baseline 3</td>
<td></td>
</tr>
<tr>
<td>Mean baseline (n=3 × 2)</td>
<td>140/86 ± 31/17</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus group; Ht, hypertensive group; Nt, normotensive group; SBP/DBP, systolic/diastolic blood pressure (mmHg).

No significant time effect was found for baseline SBP or heart rate with the feet on the floor. Therefore, the average of all six BP readings was used for the analysis. With the legs crossed at knee level, we observed significantly higher SBP in all three groups versus legs uncrossed (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mean BPs and their changes (Δ) measured at the left arm, with crossed knees and crossed ankles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knees crossed</td>
<td>Uncrossed BP ± SD</td>
</tr>
<tr>
<td>Ht</td>
<td>140/86 ± 31/17</td>
</tr>
<tr>
<td>DM</td>
<td>130/74 ± 18/8</td>
</tr>
<tr>
<td>Nt</td>
<td>111/70 ± 15/10</td>
</tr>
<tr>
<td>All</td>
<td>129/78 ± 26/15</td>
</tr>
</tbody>
</table>

Ankles crossed
| Ht   | 140/86 ± 31/17 | 139/85 ± 31/17 | -0.9/-0.6 | -2.9–1.3/-1.5–0.3 |
| DM   | 130/74 ± 18/8 | 130/73 ± 17/7 | 0.5/-0.1 | -1.0–2.0/-1.1–0.9 |
| Nt   | 111/70 ± 15/10 | 112/70 ± 15/9 | 0.8/0.0 | -0.9–2.5/0.8–0.8 |
| All  | 129/78 ± 26/15 | 128/77 ± 26/14 | -0.1/-0.3 | -1.2–1.0/-0.8–0.2 |

BP, blood pressure; CI, confidence interval; DM, diabetes mellitus group; Ht, hypertensive group; Nt, normotensive group; SBP/DBP, systolic/diastolic blood pressure (mmHg).
DM patients and Ht showed the highest increase caused by crossing the legs at the knee, especially for the SBP (+7.9 mmHg in the DM, and +6.7 mmHg in the Ht). The effect for the Nt on SBP was smaller (+2.7 mmHg), but still significant. The DBP changes in the Ht and DM group were smaller than for SBP (Table 3), however still significant. In the Nt group no rise in DBP was seen. Figure 2 shows the changes in SBP and DBP for each individual in each group.

Fig. 2

Individual changes in systolic blood pressure (upper panel) and diastolic blood pressure (lower panel) in the three groups with the mean and the 95% confidence intervals when legs are crossed at the knee. DM, diabetes mellitus group; Ht, hypertensive group; Nt, normotensive group; SBP/DBP, systolic/diastolic blood pressure (mmHg).
Crossing at the ankle did not induce any significant change in the BP readings of all three groups (Table 3). Crossing the legs at the knees resulted in a rise 5–10mmHg of SBP in 29 participants (26%), 10–20mmHg in 25 participants (23%) and >20mmHg in six participants (5%). For DBP the rise was 5–10mmHg in 14 participants (13%), 10–20mmHg in three participants (3%) and >20mmHg in one participant (1%). Apart from one case, all rises of SBP or DBP >10mmHg were in DM and Ht participants.

Men and women did not differ with regard to the change in BP when crossing the legs. No relation was found between baseline BP or age as a continuous variable and the increase of BP when crossing legs at knee level. No significant correlation of BMI and BP change with crossing the legs at the knees for the three groups was found, after correction for the other variables. No significant differences were found when BMI was stratified (<30, >30), or age was stratified (<35, 35–60, >60 years).

**Discussion**

This study clearly shows that crossing the legs at knee level significantly increased BP in Ht and DM participants. In the Nt group only the SBP showed a significant increase. The differences found are relevant both from an epidemiological and from a clinical point of view, as can be seen from the large amount of misclassifications in the study population. Further, this study shows that crossing the legs at the ankles has no significant influence on BP. Five groups have examined the effects of crossing the legs at the knees on BP measurement and are summarized in Table 4.

<table>
<thead>
<tr>
<th>Table 4 Review of the literature about the effect of crossing legs on the blood pressure measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refs.</td>
</tr>
<tr>
<td>[8]</td>
</tr>
<tr>
<td>[9]</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>[10]</td>
</tr>
<tr>
<td>[11]</td>
</tr>
<tr>
<td>[12]</td>
</tr>
<tr>
<td>Our study</td>
</tr>
</tbody>
</table>

Four studies showed a BP rise when crossing the legs; however, a broad range of BP rise was present. One of these five studies showed no influence of crossing the legs on BP. Overviewing the limited literature about this subject, most studies have some drawbacks, like more than one observer and one BP reading per leg position. Only one study has investigated the effect of different ways of crossing the legs. There was not always a proportional group of participants regarding sex, age or treatment status of hypertension. Some studies did not randomize for leg position or mention SD or 95% CIs.

In our study, the protocol was performed by one single trained investigator and multiple BP readings were done per crossed leg position and with the feet flat on the floor. The sequence of the crossing positions was randomized and all important statistical data were mentioned. Other strong points of our study are that we have investigated two crossing
positions, of which one (crossing at the ankles) is frequently practiced and unnoticed. We examined both treated Ht patients and Nt. In addition, DM participants participated in this study.

Our present study, which had a rigorously standardized study protocol, supports the findings of most other studies and adds the fact that ankle crossing has no significant effect on BP. A limitation of our study is that the investigator was not blinded for leg position. However, an automatic device was used, thereby limiting observer bias.

The rise in BP with the legs crossed might be explained by a translocation of blood from dependent vascular beds in the legs to the central thoracic compartment causing a higher stroke volume and cardiac output and thereby a rise in BP [8,10,12,16]. Another explanation could be that isometric exercise of the leg muscles increases peripheral vascular resistance and BP [9,17,18]. This possibly explains why no rise in BP is present when crossing the legs at the ankles. As for the relation of BMI and the increase of BP, we hypothesize that smaller and obese patients with more abdominal fat and with fatter upper legs could have more difficulty in maintaining their crossed leg position. This could cause an extra rise of BP caused by isometric exercise of the muscles. Unfortunately, we have not measured the exact upper leg circumference in our study. No clear explanation can be found for the observation that Nt patients have a smaller rise in BP when crossing the legs at the knee. However, it remains possible that differences in BMI, baseline BP and age may account the smaller effects in the Nt participants.

In conclusion, in the Ht and DM participants, a clinically relevant increase in BP in sitting position with crossed knees was observed. In Nt patients there was a smaller change than in the Ht and DM only in the SBP, but still clinically significant. No change was found in BP with crossing the legs at the ankles. The results of this study argue to standardize the leg position during BP measurements. The position of the legs should therefore explicitly be defined in the guidelines about hypertension and in all publications about BP measurement.
References

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Part 1

Aspects of the procedure of blood pressure measurement

Chapter 2.3

Which physiological mechanism is responsible for the increase in blood pressure during leg crossing?

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Jaap Deinum

*Journal of Hypertension* 2008; 26:433–437
Abstract

Objective To determine which physiological mechanism is responsible for the blood pressure increase during leg crossing at knee-level in the sitting position.

Methods Finger blood pressure was measured with the Finometer in 102 participants (47 men) before and during leg crossing: 24 treated hypertensive patients, 50 diabetic individuals (25 with and 25 without antihypertensive medication) and 28 healthy volunteers. Mean age was 53 ± 15 years (range 21–82 years). All participants crossed their legs at knee-level, with the upper part of the popliteal fossa on the suprapatellar bursa, in the sitting position. Differences in mean blood pressure, cardiac output, stroke volume, heart rate and total peripheral resistance were assessed with legs crossed versus legs uncrossed.

Results Mean blood pressure [+3.3 ± 5.5 mmHg; 95% confidence interval (CI) = 2.7–3.8], stroke volume (+7.6 ± 5.4 ml; 95% CI = 6.7–8.6) and cardiac output (+0.4±0.9 l/min; 95% CI = 0.3–0.5) were significantly higher with legs crossed than in the uncrossed position, while the heart rate (−1.8 ± 3.9 beats/min; 95% CI = −2.2 to −1.4) was significantly lower. Total peripheral resistance did not differ significantly (−0.01±0.16 AU; 95% CI = −0.03 to 0.00). The largest differences occurred in the hypertensive diabetic individuals, the smallest in the healthy volunteers. The changes were similar in men and women. There were no significant correlations in the total group between the differences of the hemodynamic variables and sex, age, body mass index or leg circumference.

Conclusion The study shows that higher blood pressure with legs in the crossed position is due to higher cardiac output and not to a higher total peripheral resistance.
**Introduction**

Blood pressure (BP) measurement is one of the most widely used diagnostic tests in medicine. Numerous factors can affect the outcome of a BP measurement. An erroneously measured high BP may lead to a false diagnosis of hypertension. This error can be caused by an arm position below heart level, noise, talking and movements during BP measurement and by smoking or caffeine use before BP measurement [1–3].

Another potential interfering factor resulting in a falsely high BP is leg crossing at knee level in the sitting position during BP measurement. Several, but not all, studies have shown that BP is higher when the legs are crossed at knee level in the sitting position during BP measurement [4–9]. Some studies in patients with vasovagal syncope or autonomic failure [10–12] demonstrated that the higher BP in these patients during leg crossing in a standing position with active muscle tensing is due to a higher cardiac output (CO). The aim of the present study was to determine which physiological mechanism is responsible for the higher BP during leg crossing without active muscle tensing in the sitting position in healthy volunteers and in hypertensive and diabetic patients.

**Materials and methods**

**Sample**

We included 108 participants – 28 healthy volunteers, 28 treated hypertensive patients, 52 diabetic individuals (type I and type II, 26 with and 26 without antihypertensive medication) who visited the outpatient clinic at the University Medical Centre St Radboud in Nijmegen during a 4-week period in May–June 2006.

Individuals were excluded if they were unable to cross their legs or had a history of peripheral vascular disease. Other exclusion criteria were pregnancy and arrhythmias. There were no restrictions with regard to medication.

Informed consent was obtained from all participants before the start of this study. The local ethics committee approved the protocol.

**Measurement of blood pressure**

The age, height, weight, body mass index, sex, circumference of the calf (10 cm below the patella), and circumference of the thigh (15 cm above the patella) were noted in all individuals.

BP measurements were carried out by one trained investigator in the outpatient clinic. Beat-to-beat systolic BP and diastolic BP were measured continuously and noninvasively by use of the Finometer Model 1.10 (TNO Biomedical Instrumentation, Amsterdam, The Netherlands). Finometer recordings accurately reflect BP changes [13–17]. The finger cuff was applied to the midphalanx of the left middle finger. To avoid hydrostatic level differences, the hand was continuously positioned at right atrial level in the midaxillary line.

Patients were seated in a comfortable chair with stable head, back and arm support. The individual was instructed to refrain from talking or movement during the procedure. The investigator left the room after the patient took the uncrossed leg position with both feet flat on the floor. After 7 min the investigator entered the room and the BP measurement by Finometer was started. After 3 min in the uncrossed position, the participants had to cross
their legs at knee level for 4 min (the upper part of the popliteal fossa on the suprapatellar bursa). Subsequently there was another 4-min uncrossed period. After that, the participants had to cross their legs at knee level for 4 min again. Finally they took an uncrossed position for 4 min.

The sequence of leg crossing (right/left or left/right order) was randomized.

**Stroke volume and total peripheral resistance computation.**
From the continuous BP measurement, the arterial pulse wave was analyzed by the pulse wave analysis method, which computes changes in left ventricular stroke volume (SV) from the pulsatile systolic area. We used the Modelflow program (described in [18]), which comes with the software package the manufacturer of the finometer provides with the instrument. Modelflow is a model-based algorithm that computes the aortic flow waveform from an arterial blood pressure pulsation by simulating a nonlinear, self-adaptive (three-element Windkessel) model of the aortic input impedance. Although Modelflow is less suitable to measure absolute values of SV, various studies have shown that Modelflow is a reliable method to assess changes in SV [19], which is the aim of our study. The CO was computed as the SV multiplied by the heart rate (HR). The total peripheral resistance (TPR) was calculated as the mean arterial pressure (MAP) divided by the CO and expressed in arbitrary units. The MAP was obtained as the integral of pressure over one beat divided by the corresponding interbeat interval.

**Analysis**
In the pilot phase of our study we observed that during the leg crossing itself and immediately thereafter the BP showed temporarily an extra increase for 1–2 min and then decreased to a lower steady state, but was still clearly above the BP before crossing. We therefore analyzed the last 2 min of each 4-min period of sitting with crossed or uncrossed legs. Changes for parameters are presented as the mean_SD. Reproducibility was determined by the standard deviation of the difference between the first and the second period of crossing the legs.

For statistical analysis, we used SPSS version 14.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to determine the distribution of all hemodynamic variables.

The differences in hemodynamic variables between both positions were tested by Student’s t-test (paired). The correlations between the different variables were analyzed by Pearson’s linear correlation. To account for multiple testing, Bonferroni correction was used. The influence of age, gender, body mass index, leg circumference and the presence of hypertension or diabetes mellitus on the effects of the maneuvers on the hemodynamic variables was analyzed by univariate regression. Since diabetes mellitus and hypertension had a significant effect on the changes in hemodynamic parameters, we also investigated whether antihypertensive medication modified this response. To this end we introduced an interaction term of type of medication and the presence of diabetes mellitus and/or hypertension in the regression equation.

A P value less than 0.05 was considered significant (twosided).

**Results**
Finally 102 participants were included in this study; six participants had to be excluded because of atrial flutter (n=1) or an inability to cross legs for 2 x 4 min (n=5). Patient
characteristics are presented in Table 1. All hypertensive individuals used antihypertensive medication, with a mean of 2.9 antihypertensive drugs per patient in the hypertensive group and 2.4 antihypertensive drugs per patient in the hypertensive diabetic group.

All hemodynamic variables were normally distributed as demonstrated by the Kolmogorov–Smirnov test.

Leg crossing at knee level caused a significant rise in the MAP (+3.3 mmHg, +3.6%), systolic BP (+6.6 mmHg, +5.4%) and diastolic BP (+1.4 mmHg, +2.0%) in the total study group. This rise in BP was accompanied by a significant increase in SV and CO by, respectively, +7.4 ml (8.5%) and 0.4 l/min (6.7%). The HR decreased significantly (−1.8 beats/min, −2.4%). TPR did not change significantly (−0.01 AU, −1%) (Figs 1 and 2).

**Table 1**  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total group</th>
<th>Healthy volunteers</th>
<th>Treated hypertensive patients</th>
<th>Normotensive diabetic individuals</th>
<th>Treated hypertensive diabetic individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>102</td>
<td>28</td>
<td>24</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Men/women</td>
<td>48/56</td>
<td>12/16</td>
<td>11/13</td>
<td>12/13</td>
<td>11/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53±10 (21–82)</td>
<td>48±10 (21–74)</td>
<td>60±10 (22–82)</td>
<td>47±10 (22–76)</td>
<td>58±11 (41–81)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80±5</td>
<td>70±5</td>
<td>81±5</td>
<td>78±5</td>
<td>87±5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174±5</td>
<td>174±5</td>
<td>173±5</td>
<td>176±5</td>
<td>173±5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27±5 (20–41)</td>
<td>26±5 (20–32)</td>
<td>27±5 (22–31)</td>
<td>25±5 (20–31)</td>
<td>29±5 (20–41)</td>
</tr>
<tr>
<td>Leg circumference, calf (cm)</td>
<td>37±4</td>
<td>37±4</td>
<td>36±4</td>
<td>38±2</td>
<td>37±4</td>
</tr>
<tr>
<td>Leg circumference, thigh (cm)</td>
<td>47±4</td>
<td>47±4</td>
<td>47±5</td>
<td>46±3</td>
<td>48±5</td>
</tr>
<tr>
<td>Baseline SBP/DBP (mmHg)*</td>
<td>122/68 ±20/11</td>
<td>118/69 ±17/10</td>
<td>130/72 ±25/13</td>
<td>120/66 ±17/7</td>
<td>121/66 ±18/11</td>
</tr>
</tbody>
</table>

Data presented as the mean ± SD (range). *Mean of the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) in the three uncrossed positions measured by Finometer.

All hemodynamic variables were normally distributed as demonstrated by the Kolmogorov–Smirnov test.

Leg crossing at knee level caused a significant rise in the MAP (+3.3 mmHg, +3.6%), systolic BP (+6.6 mmHg, +5.4%) and diastolic BP (+1.4 mmHg, +2.0%) in the total study group. This rise in BP was accompanied by a significant increase in SV and CO by, respectively, +7.4 ml (8.5%) and 0.4 l/min (6.7%). The HR decreased significantly (−1.8 beats/min, −2.4%). TPR did not change significantly (−0.01 AU, −1%) (Figs 1 and 2).

**Fig. 1**

Time course of the mean arterial pressure (MAP, ●), cardiac output (CO, △) and total peripheral resistance (TPR, ○). Boxes refer to leg crossing at the knee position. Data are the mean ± SE of 1 min of measurement.
All subgroups showed the same trend in hemodynamic differences. Although the differences in MAP, SV, CO and HR were largest in the hypertensive diabetic individuals (+4.0 mmHg, +10.6 ml, +0.7 l/min and −1.0 beats/min, respectively) and lowest in the healthy volunteers (respectively +2.2 mmHg, +4.7 ml, +0.1 l/min and −2.9 beats/min), the differences in all subgroups were significant. All results are presented in Tables 2 and 3.

Table 2  Differences in hemodynamic parameters between uncrossed and crossed leg positions in the total study group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Uncrossed leg position</th>
<th>Crossed leg position</th>
<th>Difference absolute (relative)</th>
<th>(95% confidence interval of absolute difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>123.1 ± 10.5</td>
<td>129.7 ± 19.2</td>
<td>+6.6 (+5.4%)</td>
<td>(5.8/7.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>66.9 ± 10.6</td>
<td>70.3 ± 9.9</td>
<td>+1.4 (+2.0)</td>
<td>(1.3/2.1)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>90.1 ± 13.0</td>
<td>93.4 ± 12.4</td>
<td>+3.3 (+3.6%)</td>
<td>(2.7/3.8)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72.1 ± 12.6</td>
<td>70.0 ± 12.3</td>
<td>−1.8 (−2.4%)</td>
<td>(−2.2/−1.4)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>88.6 ± 24.3</td>
<td>96.4 ± 26.5</td>
<td>+7.8 (8.5%)</td>
<td>(6.7/8.6)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.3 ± 1.7</td>
<td>6.7 ± 1.9</td>
<td>+0.4 (+6.3%)</td>
<td>(0.3/0.5)</td>
</tr>
<tr>
<td>Total peripheral resistance (AU)</td>
<td>0.94 ± 0.37</td>
<td>0.93 ± 0.36</td>
<td>−0.01 (−1%)</td>
<td>(−0.03/0.00)</td>
</tr>
</tbody>
</table>

Leg position data presented as the mean ± SD.

Men and women did not differ with regard to the increase in BP or any other hemodynamic variables. There was no significant difference in the MAP either if the sequence was left/right or right/left. The difference in the MAP between the first and the second leg crossings was 0.6±1.2 mmHg. The difference in CO between the first and the second leg crossings was 0.02±0.6 l/min, indicating adequate reproducibility of the test. Both in the total study group and in the subgroups we observed a positive correlation between the difference in MAP and the difference in CO, varying from r=0.17 (P=0.36) in the normotensive individuals to r=0.67 (P<0.05) in the hypertensive diabetic participants. For the total study group we observed no correlation between the differences in CO and their baseline value, body mass index, age or leg circumference. By regression analysis with the difference in CO, the difference in HR or
the difference in SV as dependent variables, we found a significant influence of the diagnosis hypertension (for changes in CO and HR), of diabetes mellitus (for changes in CO and SV) and of diabetes and/or hypertension (for changes in all three variables). The use of different antihypertensive drugs, however, studied as an interaction term with the presence of hypertension, diabetes mellitus or their combination, could not explain the hemodynamic changes in a model that included the presence of hypertension, diabetes mellitus or their combination (results not shown).

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>Healthy volunteers</th>
<th>Treated hypertensive patients</th>
<th>Normotensive diabetic individuals</th>
<th>Treated hypertensive diabetic individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in systolic blood pressure (mmHg)</td>
<td>+4.1 ± 6.8 (2.8–5.4)</td>
<td>+7.0 ± 7.4 (5.5–8.5)</td>
<td>+7.8 ± 7.2 (6.4–9.3)</td>
<td>+8.2 ± 10.7 (6.1–10.4)</td>
</tr>
<tr>
<td>Difference in diastolic blood pressure (mmHg)</td>
<td>+1.2 ± 3.2 (0.6–1.8)</td>
<td>+1.4 ± 3.3 (0.6–2.1)</td>
<td>+2.1 ± 3.4 (1.4–2.6)</td>
<td>+2.2 ± 4.3 (1.4–3.1)</td>
</tr>
<tr>
<td>Difference in mean arterial pressure (mmHg)</td>
<td>+2.2 ± 4.1 (1.4–2.9)</td>
<td>+3.6 ± 4.6 (2.6–4.5)</td>
<td>+3.9 ± 4.7 (2.9–4.8)</td>
<td>+4.0 ± 6.4 (2.7–5.2)</td>
</tr>
<tr>
<td>Difference in heart rate (beats/min)</td>
<td>−2.9 ± 3.5 (−3.6 to −2.3)</td>
<td>−1.1 ± 4.2 (−1.9 to −0.2)</td>
<td>−2.0 ± 3.7 (−2.7 to −1.3)</td>
<td>−1.0 ± 3.7 (−1.8 to −0.3)</td>
</tr>
<tr>
<td>Difference in stroke volume (ml)</td>
<td>+4.7 ± 6.0 (2.4–5.8)</td>
<td>+6.0 ± 8.4 (5.1–8.5)</td>
<td>+8.5 ± 8.1 (8.0–10.1)</td>
<td>+10.6 ± 10.3 (8.5–12.6)</td>
</tr>
<tr>
<td>Difference in cardiac output (l/min)</td>
<td>+0.1 ± 0.4 (0.0–0.2)</td>
<td>+0.4 ± 0.5 (0.3–0.5)</td>
<td>+0.4 ± 0.4 (0.3–0.5)</td>
<td>+0.7 ± 0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>Difference in total peripheral resistance (AU)</td>
<td>+0.01 ± 0.07 (0.00–0.02)</td>
<td>0.03 ± 0.18 (0.00–0.06)</td>
<td>−0.01 ± 0.07 (−0.02 to 0.01)</td>
<td>−0.02 ± 0.35 (−0.06 to 0.05)</td>
</tr>
</tbody>
</table>

Data presented as the mean ± SD.

Discussion
The present study shows that, both in healthy individuals and in patients with hypertension and diabetes mellitus, the higher BP during leg crossing at knee level is due to a higher CO and not to a higher TPR. The rise in CO is due to an increase in the SV. An explanation of this increase in SV and reaching a steady state is the translocation of blood to the central thoracic compartment by continuous mechanical compression of venous capacitance vessels in the leg. The significant decrease in the HR is due to a baroreceptor reflex activation as a consequence of the increase in blood pressure. A smaller decrease in the HR is seen in the hypertensive and hypertensive-diabetic subgroups.

Our results are in agreement with the conclusions from Krediet et al. [10] and van Dijk et al. [11] in patients with vasovagal syncope and autonomic dysfunction in the standing position with active muscle tensing. In these studies the BP measurement was started directly after performing the maneuver and took 2 min. In a previous pilot study [9] we observed that BP stabilized 2 min after changing leg position. For this reason, and because Wieling et al. [20] showed a blood pressure response immediately after starting dynamic leg exercise in humans, we only analyzed the BP values of the last 2 min of each position.

Groothuis et al. [21] suggested that leg crossing increases TPR mechanically. Their study, however, reports leg crossing with muscle tensing in a standing position. In our study, participants had to cross their legs in a sitting position without muscle tensing. Comparing the results of these studies is therefore not possible because of the study design differences.

Continuous beat-to-beat BP measurement is a strong point of the present study, because changes in hemodynamic variables were calculated based on a great number of measurements. We examined a large number of participants with different cardiovascular risk factors. The reason why we examined four subgroups is inspired by the potential influence of both underlying disease and the medication on the changes in hemodynamic variables. The randomization of leg order is important, because when there is no randomization participants take their ‘preferential position’.
We did not consider or correct for the influence of meals, coffee, smoking and the time of medication intake. Possibly there is a relation between the time of meals, coffee, smoking or medication intake and the time of BP measurement.

Changes in CO were related to the presence of hypertension, diabetes mellitus and their combination, but were not explained by the use or the type of the antihypertensive drug. Further analysis was limited by the fact that the patients were on many different combinations of antihypertensive drugs we could not adequately test for interactions of drugs.

Hypertensive and/or diabetic individuals show the most pronounced hemodynamic response to changing leg position, whereas healthy volunteers show the smallest response. This difference cannot be attributed to different subgroup characteristics or to the use of antihypertensive treatments. The subgroups may have been too small, however, to rule out an effect of antihypertensive drugs. A physiological explanation for the pronounced response in hypertensive and/or diabetic individuals could be the decreased venous distensibility that is already present in borderline hypertensive patients [22]. If crossing the legs causes compression of the capacitance vessels, the ensuing mobilization of blood from the legs can be contained to a lesser extent in the relatively stiffer venous vessels, leading to increased venous return and, hence, to increased CO.

In conclusion, the present study shows that a higher BP during leg crossing at knee level is due to the higher CO and not to a higher TPR. The results of this study suggest the importance of standardizing the leg position during BP measurements. The position of the legs should therefore be explicitly reported in the guidelines about hypertension and in all publications about BP measurement.

Acknowledgements
There are no conflicts of interest.
References

1 Netea RT, Thien T. Blood pressure measurement: we should all do it better!. Neth J Med 2004; 62:297–303.
8 Avvampato CS. Effect of one leg crossed over the other at the knee on blood pressure in hypertensive patients. Nephrol Nurs J 2001; 28:325–329.
Part 2

Progression of blood pressure measurement

Chapter 3.1

Thirty years of research on diagnostic and therapeutic thresholds for the self-measured blood pressure at home.

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Lutgarde Thijs
Takayoshi Ohkubo
Masahiro Kikuya
Tom Richart
José Boggia
Ahmet Adiyaman
Dirk G. Dechering
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Theo Thien
Peter de Leeuw
Yutuka Imai
Eoin O'Brien
Gianfranco Parati

Abstract

Objective The goal of this review study is to summarize 30 years of research on cut-off limits for the self-measured blood pressure.

Methods We reviewed two meta-analyses, several prospective outcome studies in populations and hypertensive patients, studies in pregnant women, three clinical trials and the thresholds proposed in earlier and current hypertension guidelines.

Results In line with existing guidelines, prospective studies support that levels of the self-measured blood pressure at home of greater than or equal to 135mmHg systolic or greater than or equal to 85mmHg diastolic indicate hypertension. Circumstantial data suggest that levels of the self-measured blood pressure below 120/80 and 130/85mmHg are optimal and normal, respectively. Therapeutic targets of the self-measured blood pressure to be attained on antihypertensive drug treatment are currently unknown, but should logically be lower (< 135/85mmHg) than those used to diagnose hypertension. Currently, there is no proof that therapeutic thresholds for the home blood pressure should be lower in high-risk compared with normal-risk patients. A large body of evidence, however, demonstrated that each millimetre of mercury of blood pressure lowering counts in the prevention of cardiovascular complications and that in high-risk patients even small decreases in blood pressure result in large absolute benefit.

Conclusion The thresholds to diagnose hypertension from self-measured blood pressure readings at home remain unaltered since the 2000 consensus conference, but are currently supported by outcome data. Further studies need to establish what values of the self-measured blood pressure are optimal and normal in terms of cardiovascular outcome.
Introduction

Already in 1971, investigators from Leuven promoted the use of blood pressure self-measurement at home in clinical research [1]. The development of cheap and properly validated devices for blood pressure selfmeasurement, over the past 20 years, carried this technique to clinical application [2–6]. Blood pressure self-measurement offers several of the well-recognized advantages of the more complex approach of ambulatory monitoring [7,8]. The greater number of readings [5,9] and the absence of the white coat effect [10] contribute to a better diagnostic accuracy, compared with conventional sphygmomanometry [11,12]. If automated devices are used [5], self-recorded blood pressure values are free of observer bias. Moreover, self-measurement of blood pressure increases adherence to antihypertensive treatment [13,14] and allows reducing the number of clinic visits required for the diagnosis and treatment of hypertension [15–17].

The goal of the current review study is to summarize over 30 years of research on cut-off limits for the selfmeasured blood pressure. We reviewed the literature in preparation of the second consensus meeting on the selfmeasured blood pressure, which took place in Verbania, Italy, on 13–14 June 2007. The European Society of Hypertension recently published its new guidelines, based on the second consensus conference [18].

For this study, we reviewed two meta-analyses [19,20], several prospective outcome studies in populations [21–31] and hypertensive patients [32–36], studies in pregnant women [37–41], children and adolescents [42–45], and three clinical trials [46–48] exploring adjustment of antihypertensive drug treatment guided by the self-measured blood pressure at home. We next reviewed the operational thresholds for the self-measured blood pressure as proposed by hypertension guidelines before June 2007 [49–62]. We conclude with the proposals we put forward for discussion at the second consensus meeting.

Evidence from two meta-analyses

In an attempt to define diagnostic thresholds for the selfmeasured blood pressure, we performed in collaboration with a large number of researchers two meta-analyses [19,20], which were respectively based on aggregate data extracted from published articles [19] and on individual patient data, made available to the International Database of Self-Recorded Blood Pressures [20].

Aggregate data extracted from published articles

In 1998, we reviewed 17 studies [1,63–78] including a total of 5422 participants. The number of participants in each of the individual studies ranged from 14 [63] to 1438 [75]. Eight reports did not apply any selection criteria based on blood pressure values [1,67,68,71,73,75,76,78]. Mean age ranged from 16 [72] to 47 years [78]. The participants measured their blood pressure by an automatic or semiautomatic oscillometric device in five studies [66–68,75,78], by a semiautomatic auscultatory device in four reports [64,72,76,77], or by a manual sphygmomanometer in eight reports [1,63,65,69–71,73,74]. In most studies, participants measured their blood pressure over several days (range, 1–63 days), usually in the morning and evening. The number of self-recorded blood pressures averaged for analyses ranged from 2 [75] to 252 [1].

With weighing for the number of participants included in the various studies, the self-recorded blood pressure averaged 115/71mmHg in normotensive participants and 119/74mmHg in untreated participants not selected on the basis of their blood pressure [19].
Within each study, we computed an operational threshold for the self-measured blood pressure separating normotension from hypertension from the mean + 2 standard deviations or from the 95th percentile of the self-recorded blood pressure in participants who were normotensive according to their office blood pressure (Table 1). For sake of comparability with the contemporary literature, we also extracted from published studies thresholds derived by the regression approach or the percentile method. The former consists of calculating the regression line between the self-recorded blood pressure and the clinic blood pressure in individual patients to estimate the self-recorded blood pressure that corresponds with a clinic blood pressure of 140mmHg systolic or 90mmHg diastolic [19]. The percentile method involves first the calculation of the percentile of the clinic blood pressure that corresponds to 140mmHg systolic or 90mmHg diastolic and next the determination of the self-recorded blood pressure that ranks at the same percentile value [19].

The reference values for the self-recorded systolic/diastolic blood pressures as derived from the mean + 2 standard deviations (137/89 mmHg) and the 95th percentile (135/86 mmHg) of the distribution in normotensive participants were concordant within 2mmHg systolic and 3mmHg diastolic. The cut-off points derived using the regression and percentile methods were considerably lower, that is, 129/84 and 125/79mmHg, respectively [19].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Operational cut-off points between ‘normotension’ and ‘hypertension’ for self-recorded blood pressure in individual studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Self-measured blood pressure corresponding to an office blood pressure of 140/90 mmHg</td>
</tr>
<tr>
<td></td>
<td>Percentile method</td>
</tr>
<tr>
<td>Bättig et al. [64]</td>
<td>NA</td>
</tr>
<tr>
<td>Beckman et al. [65]</td>
<td>NA</td>
</tr>
<tr>
<td>Brody and Rau [66]</td>
<td>NA</td>
</tr>
<tr>
<td>De Gaudemaris et al. [67]</td>
<td>127/83</td>
</tr>
<tr>
<td>Imai et al. [68]</td>
<td>128/84</td>
</tr>
<tr>
<td>James et al. [63]</td>
<td>NA</td>
</tr>
<tr>
<td>Johnson [69]</td>
<td>NA</td>
</tr>
<tr>
<td>Julius et al. [70]</td>
<td>NA</td>
</tr>
<tr>
<td>Julius et al. [71]</td>
<td>?</td>
</tr>
<tr>
<td>Kawabe et al. [72]</td>
<td>NA</td>
</tr>
<tr>
<td>Kosteloot et al. [73]</td>
<td>?</td>
</tr>
<tr>
<td>Kjeldsen et al. [74]</td>
<td>NA</td>
</tr>
<tr>
<td>Mancia et al. [75]</td>
<td>?</td>
</tr>
<tr>
<td>Mengden et al. [76]</td>
<td>?</td>
</tr>
<tr>
<td>Saito et al. [77]</td>
<td>NA</td>
</tr>
<tr>
<td>Weisser et al. [78]</td>
<td>133/86</td>
</tr>
</tbody>
</table>

NA indicates not applicable because the study included only normotensive participants. Question mark indicates that the information was unavailable. Reproduced with permission from ref. [19].

a Weighed mean of reference values obtained in eight sex–age strata.
Individual patient data as available in the international database

Thirteen research groups contributed 4668 untreated participants to the International Database [20], of whom 2401 were normotensive on office measurement. Participants had their office blood pressure measured at one (79%), two (18%) or three (3%) occasions. They were characterized by only one office blood pressure reading in a small minority (0.2%) or the average of two (39.7%), three (38.9%), four (4.4%) or six (16.7%) office blood pressure readings. Participants recorded their blood pressure over a median of 3 days, obtaining from 1 to 159 readings (median, 14). The self-recorded blood pressure in the total study population averaged 129.9mmHg systolic and 79.8mmHg diastolic. Among 3221 participants, whose morning and evening blood pressures were separately available, systolic blood pressure was on average 1.9mmHg higher (P<0.001) in the morning with no diurnal difference in the diastolic blood pressure. Figure 1 illustrates the associations of the conventional and self-measured blood pressure with age.

![Figure 1](image)

The mean self-recorded blood pressure in 2401 normotensive participants averaged 115.4mmHg systolic and 70.7mmHg diastolic. The 95th percentiles of their self-recorded blood pressures were 136mmHg systolic and 85mmHg diastolic in the morning, 139 and 86mmHg in the evening and 137 and 85mmHg over the whole day.
The database included 2267 hypertensive participants, of whom 494 participants had only a borderline elevation of their systolic or diastolic blood pressure (140–159/90–94 mmHg), and 1773 participants were definitely hypertensive (≥160 systolic or ≥95 mmHg diastolic). By definition, there was a difference of at least 20 mmHg systolic or 5 mmHg diastolic between the office blood pressure of normotensive participants and patients with definite hypertension. Nevertheless, there was considerable overlap in the distributions of the self-measured blood pressure of normotensive and hypertensive participants (Fig. 2).

Of 1773 patients with definite systolic hypertension on office measurement (see above), 16% had a self-measured systolic blood pressure below 137 mmHg (the 95th percentile of the self-measured systolic pressure in normotensive participants). Similarly, 25% of those with definite diastolic hypertension had a self-measured diastolic blood pressure below 85 mmHg (the 95th percentile of the self-measured diastolic pressure in normotensive participants). The probability that participants with definite hypertension had a self-measured blood pressure below these thresholds (isolated office hypertension or white-coat hypertension [79]) was 34% (diastolic) to 62% (systolic) greater in women than in men. It was two-fold to three-fold greater if fewer than three office blood pressure readings had been averaged to diagnose
hypertension, and it increased by 50 (diastolic) to 126% (systolic) if the self-measured blood pressure had been measured on more than 3 days as opposed to fewer days (Table 2). In contrast, for each 10-mmHg increment in the systolic office blood pressure, the probability of isolated office systolic hypertension decreased by 35%; for each 5-mmHg increment in the diastolic office blood pressure, the probability of isolated office diastolic hypertension diminished by 36%. Finally, the probability of isolated office systolic hypertension fell by 31% for each 10-year increment in age (Table 2).

### Table 2  Odds ratios expressing the probability that patients with definite hypertension have a self-measured blood pressure below the 95th percentile in participants with office normotension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Systolic hypertension</th>
<th>Diastolic hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in analysis</td>
<td>1070</td>
<td>1634</td>
</tr>
<tr>
<td>Odds ratios (95% confidence interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women versus men</td>
<td>1.82 (1.14–2.30)</td>
<td>1.34 (1.05–1.70)</td>
</tr>
<tr>
<td>10 years older</td>
<td>0.69 (0.59–0.81)</td>
<td>NS</td>
</tr>
<tr>
<td>5 kg/m² higher body mass index</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>10 mmHg higher office systolic blood pressure</td>
<td>0.65 (0.53–0.80)</td>
<td>0.89 (0.82–0.97)</td>
</tr>
<tr>
<td>5 mmHg higher office diastolic blood pressure</td>
<td>NS</td>
<td>0.64 (0.56–0.73)</td>
</tr>
<tr>
<td>≤ 2 versus more office readings</td>
<td>2.99 (1.67–5.33)</td>
<td>2.29 (1.52–3.45)</td>
</tr>
<tr>
<td>&gt;3 versus ≤ 3 days of self-measurement</td>
<td>2.26 (1.49–3.41)</td>
<td>1.50 (1.12–2.01)</td>
</tr>
</tbody>
</table>

The odds ratios were mutually adjusted for all explanatory variables in the Table. NS, nonsignificant.

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### Evidence from prospective studies


### Table 3  Thresholds proposed in prospective cohort studies

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Year</th>
<th>Sample</th>
<th>Number</th>
<th>Age</th>
<th>Readings (days)</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohama [21–23]</td>
<td>1997–2006</td>
<td>P</td>
<td>1913</td>
<td>60.8</td>
<td>&gt;40</td>
<td>M (28)</td>
</tr>
<tr>
<td>Kouchu [33–34]</td>
<td>1999</td>
<td>P</td>
<td>1186</td>
<td>73.5</td>
<td>&gt;65</td>
<td>M/E (5)</td>
</tr>
<tr>
<td>Rave et al. [32]</td>
<td>2000</td>
<td>P</td>
<td>401</td>
<td>80.0</td>
<td>&gt;75</td>
<td>M/E (5)</td>
</tr>
<tr>
<td>SHEAF [38]</td>
<td>2004</td>
<td>HM</td>
<td>4959</td>
<td>70</td>
<td></td>
<td>M/E (4)</td>
</tr>
<tr>
<td>Aguirre [36]</td>
<td>2006</td>
<td>CVD</td>
<td>217</td>
<td>67.4</td>
<td></td>
<td>M/E (7)</td>
</tr>
<tr>
<td>Dido [31]</td>
<td>2007</td>
<td>P</td>
<td>666</td>
<td>54.1</td>
<td></td>
<td>M/E (3)</td>
</tr>
</tbody>
</table>

Number indicates the number of patients enrolled with the proportion of women given between parentheses. M, A and E stand for morning, afternoon and evening with the number of measurement days given between parentheses.

CKD, patients with chronic kidney disease; DM, patients with diabetes mellitus; HT, patients with hypertension; P, population sample; PAMELA, Pressioni Arteriosse Monitorate e Loro Associazioni; SHEAF, Self-measurement of blood pressure at Home in the Elderly: Assessment and Follow-up.
The Ohasama study
The Japanese investigators of the Ohasama study were the first to demonstrate that the self-measured blood pressure at home is a more precise predictor of outcome than the office blood pressure [21,22,25] and in consecutive publications [21–28] proposed and refined diagnostic thresholds for its use in clinical practice.

The Ohasama researchers initially proposed 137mmHg systolic and 84mmHg diastolic as acceptable upper limits for home blood pressure readings on the grounds that the risk of death increased above these thresholds [21]. These levels were comparable with the thresholds previously suggested by an international research consortium (137/85mmHg [20]). Rounding these thresholds [20,21] to 135mmHg systolic and 85mmHg produced diagnostic limits similar to those in the meta-analysis of aggregate data [19] and in several guidelines [49,50,57,62].

The Japanese investigators subsequently published a subgroup analysis of Ohasama residents with and without cardiovascular risk factors, including diabetes mellitus, hypercholesterolaemia, habitual smoking and a history of cardiovascular disease [26]. In high-risk patients, prehypertension arbitrarily defined as a self-measured blood pressure ranging from greater than or equal to 115mmHg to less than 135mmHg systolic or from greater than or equal to 75 to less than 85mmHg diastolic, compared with normotension, carried a two-fold higher risk of stroke. These observations suggested that the thresholds of the home blood pressure applicable to high-risk patients might be lower than 135/85mmHg [26].

The Ohasama investigators [27] also reported the incidence of stroke according to the level of the office and home blood pressures after stratification for cardiovascular risk based on the criteria jointly proposed by the European Society of Hypertension and the European Society of Cardiology [53]. The key points emerging from these analyses (Fig. 3) were that even in patients with low added risk both the office and self-measured blood pressures predicted stroke, and that across the strata of cardiovascular risk the probability of a first stroke rose steeper with the home than with the office blood pressure [27].

A recent Ohasama study noticed that the self-measured blood pressure predicted the risk of stroke, irrespective of whether it was measured in the morning or evening [28]. A level of 135/85mmHg or higher was associated with a two-fold increase in the risk of stroke compared with the subgroup with levels of the home blood pressure below 135mmHg systolic and 85mmHg diastolic in the morning and evening. The multivariate-adjusted hazard ratios amounted to 2.66 (95% confidence interval, 1.64–4.33) for hypertension in the morning, and to 2.38 (1.65–3.45) for hypertension sustained from the morning to the evening [28].

The Kahoku study
A preliminary cross-sectional analysis of the Kahoku study considered a self-measured blood pressure of 135mmHg systolic and 85mmHg diastolic as the upper limit of normality, because these levels corresponded with the mean+1 standard deviation (79th percentile) in 708 untreated participants aged from 25 to 64 years [80].

The first publication with outcome data from the Kahoku study [33] included 1186 residents, aged 65 years or older, who in 1992 measured their blood pressure at home for 5 consecutive days and whose mortality (134 deaths) was recorded over 4 years. Okumiya and colleagues [33] applied arbitrary cut-off limits to delineate four categories according to the self-measured systolic (≤124, 125–134, 135–144, ≥145mmHg) and diastolic (≤74, 75–79, 80–84,
≥85mmHg) blood pressures. In multivariate-adjusted analyses across these groups, total mortality showed a significant U-shaped association with the home systolic blood pressure in men. The lowest risk occurred at levels ranging from 125 to 134mmHg. The multivariate-adjusted associations of mortality with the categories of systolic blood pressure in women and those with the diastolic subgroups in both sexes were not statistically significant.

The 2005 Kahoku study included only 461 participants, who were at least 75 years old at enrollment (mean age, 80 years) and who were followed up for 9 years [34]. Nishinaga and colleagues [34] arbitrarily subdivided the study population in four subgroups of unequal size, depending on the level of the self-measured systolic blood pressure in the morning (<135 vs. ≥135 mmHg) and the difference between the morning and evening systolic blood pressures (<15 vs. ≥15mmHg). Participants having both lower systolic blood pressure in the morning and less diurnal variability in systolic pressure were used as reference group. With adjustments for confounders applied, high blood pressure in the morning with or without large differences between the morning and evening blood pressures predicted shorter survival and loss of independence.
The Pressioni Arteriose Monitorate e Loro Associazioni study
The Pressioni Arteriose Monitorate e Loro Associazioni study included 2051 residents of Monza (Italy), randomly recruited after stratification for sex and age (25–74 years). The participation rate was 64%. Participants obtained two readings of their self-measured blood pressure at home, one in the morning and one in the evening [29,30,75,81].

A cross-sectional analysis of 1438 participants [75], while recruitment was still ongoing, suggested that the systolic blood pressure levels at home corresponding with a clinic level of 140mmHg would across the age span (25–64 years) range from 127 to 132mmHg (upper boundary of the 95% confidence interval, 128–134 mmHg) in men, and from 121 to 126mmHg (125–129mmHg) in women. For diastolic blood pressure, the corresponding thresholds varied from 75 to 81mmHg (77–83 mmHg) in men and from 77 to 81mmHg (80–83 mmHg) in women. A later cross-sectional analysis of 248 normotensive and untreated hypertensive participants, aged 65–74 years, suggested as thresholds for the self-measured blood pressure at home levels of 133mmHg (95% confidence interval, 131–135mmHg) systolic and 82mmHg (80–83 mmHg) diastolic [81].

After an average follow-up of 131 months, 186 deaths occurred, of which 56 were cardiovascular (30.1%). Office and home blood pressures showed a significant relationship with cardiovascular and all-cause mortality, but the association was not tighter for the home than for the office blood pressure [29].

In a subsequent analysis [30], the Pressioni Arteriose Monitorate e Loro Associazioni investigators subdivided their cohort in four groups based on the office and home blood pressures, using as thresholds 140/90 and 135/83 mmHg, respectively. With normotension on both types of measurement as reference, the risk of cardiovascular and total mortality gradually increased if the office blood pressure, the home blood pressure, or both types of blood pressure were elevated. This trend was consistent in unadjusted and sex-adjusted and age-adjusted analyses.

The Didima study
Stergiou and colleagues [31] followed cardiovascular morbidity and cause-specific mortality over 8.2 years in 662 residents of Didima (Greece). Mean age at enrolment was 54.1 years and the proportion of women was 58.2%. During follow-up 78 deaths (42 cardiovascular) and 67 fatal and nonfatal events occurred. The unadjusted hazard ratios for cardiovascular events per 10mmHg increase in the systolic blood pressure were 1.41 (P<0.001) and 1.40 (P<0.001) for office and home measurements, respectively. The corresponding estimates for a 5mmHg increase in diastolic blood pressure were 1.20 (P<0.01) and 1.11 (P=0.07). The addition of the home blood pressure (average of duplicate readings in the morning and evening on 3 consecutive days) to Cox models already including the office blood pressure (average readings; three readings at each of two clinic visits) did not significantly improve the prediction of cardiovascular complications.

In categorical analyses, the Didima investigators defined office and home hypertension as systolic/diastolic blood pressure levels of 140/90 and 135/85mmHg or higher, respectively [31]. Patients with hypertension on both types of measurements (events/patients at risk, 26 of the 124 patients; 21.0%) and those with the white-coat phenomenon (nine of the 34 patients; 26.5%) had significantly higher cardiovascular risk than those who had a normal blood pressure in the office as well as at home (24 of the 452 patients; 5.3%). In contrast, masked
hypertension was not associated with a significantly higher risk (eight of the patients 55; 14.5%).

**Patient cohorts**

The Self-measurement of blood pressure at Home in the Elderly: Assessment and Follow-up study [35] enrolled 4939 treated hypertensive patients aged 60 years or older. For the office and self-measured blood pressures, the targets to be reached on antihypertensive drug treatment were levels below 140/90 and 135/85mmHg, respectively. The incidence of cardiovascular events in patients with elevated blood pressure in the office, but not at home, was the same as that in patients with controlled hypertension on both measurements: 11.1 versus 12.1 cases per 1000 patient-years, respectively. Conversely, the incidence of cardiovascular events in patients with elevated blood pressure at home, but not in the office, was high and similar to that of patients with uncontrolled hypertension on both measurements (30.6 vs. 25.6 cases per 1000 patient-years). In multivariate-adjusted models, using patients with normal office and normal self-measured blood pressures as the referent group, the hazard ratio of cardiovascular events doubled in patients with uncontrolled hypertension on both measurements (1.96; 95% confidence interval, 1.27–3.02) and in patients with an elevated blood pressure at home, but not in the office (2.06; 95% confidence interval 1.22–3.47). In contrast, patients with an elevated blood pressure in the office, but not at home, did not have an increased risk (1.18; 95% confidence interval, 0.67–2.10).

Agarwal and Andersen [36] followed 217 patients with chronic kidney disease for a median of 3.5 years, of whom 39 patients died. Of the 178 remaining patients, 38 patients developed end-stage renal disease. Poor control of the self-measured blood pressure at home, defined as a systolic level of 130mmHg or higher, was a powerful predictor of end-stage renal disease. None of the patients with a self-measured blood pressure below 130mmHg systolic, even in the presence of an elevated office blood pressure, progressed to end-stage renal disease.

Rave and coworkers [32] studied the progression of nephropathy in 71 patients with type-1 diabetes, who were followed up for 6.2 years on average. Over this period, the office and the self-measured blood pressures dropped from 166/95 to 154/89mmHg and from 159/93 to 138/83mmHg, respectively. In multivariate-adjusted analyses, the self-measured blood pressure at baseline was a strong and independent predictor of the subsequent loss in renal function. As the renal function continued to decline, Rave’s findings [32] suggest that the level of the self-measured blood pressure to target on antihypertensive drug treatment in diabetic patients might be less than 138/83 mmHg.

**Self-monitoring in pregnancy**

Accurate measurement of blood pressure by automated techniques is feasible in pregnant women [40,82]. Ambulatory blood pressure monitoring [83] and selfmeasurement of blood pressure at home [37], compared with office measurement, are more predictive of severe hypertension or proteinuria. However, there is only indirect evidence to support operational thresholds for the self-measured blood pressure in antenatal care.

Ross-McGill and colleagues [38] randomized 80 women at 24–28 weeks of their pregnancy to a standard nine-visit schedule (30, 32, 34, 36–41 weeks) or to a reduced schedule (34, 38, 41 weeks). Women with multiple pregnancies, established hypertension or a history of preeclampsia before 34 weeks, or pregnancy loss were not eligible. Women in the home-monitoring group (reduced schedule group) measured their blood pressure weekly, using a portable sphygmomanometer. They were instructed to repeat self-measurement after 4 h, if
The blood pressure level at the first reading was between 140 and 160mmHg systolic or between 90 and 100mmHg diastolic and to contact their midwife if the second reading was higher than 140mmHg systolic or 90mmHg diastolic. If any reading was higher than 160mmHg systolic or 100mmHg diastolic, women had to contact their midwife immediately. Although there were more unscheduled visits in the home monitoring group, this did not outweigh the reduction in scheduled visits (7.4 vs. 4.5; P<0.001) and blood pressure was measured during more weeks (9 vs. 7; P<0.001) in the experimental group. Most women expressed a preference for the reduced schedule both when the idea was first suggested, and after they had experienced it, and there were no significant between-group differences in anxiety.

In a subsequent study in 72 pregnant women at high risk of preeclampsia, Waugh and coworkers observed that of 979 self-measurements taken only 28 (2.9%) were inaccurate [39]. On further questioning, two women admitted that the device had been used by other family members, thus making comparison with the other measurements stored in memory impossible. Thus, the true nonconcordance rate amongst participants was 1/72 (1.4%). The same investigators, based on Stergiou’s observation that on average the home blood pressure in nonpregnant hypertensive patients is 12/7mmHg lower than the office blood pressure [5], recommended to use a threshold of 135mmHg systolic and 85mmHg diastolic to monitor the home blood pressure in pregnant women [37].

In a study by Denolle and colleagues [40], 45 healthy pregnant women measured their blood pressure for 1 week before 15 weeks of gestation, between weeks 15 and 27, and after 28 weeks for the last 3 months of gestation. The self-measured blood pressure was significantly lower during the second trimester and higher during the last trimester (102/59, 101/57, 105/62 mmHg, respectively) than during other trimesters. On the basis of the mean + 2 standard deviations, Denolle and colleagues [40], suggested as upper limits of normality 118/73, 117/73 and 121/80mmHg for the three trimesters of pregnancy.

**Self-monitoring in children and adolescents**

Self-measurement of blood pressure by children and adolescents by means of semiautomatic [84] or automatic [85] devices, specifically validated in this age group, is feasible [43,44]. Whereas in adults the self-measured blood pressure and daytime blood pressure often have approximately similar levels, in children and adolescents, the self-measured blood pressure at home is apparently lower than the daytime ambulatory blood pressure [42]. In 23 normotensive children enrolled in Stergiou’s study (mean age, 12.3 years), blood pressure levels averaged 112.8/63.1, 106.7/67.2 and 123.9/72.0mmHg on conventional, home and daytime ambulatory measurement, respectively [42]. The 2004 guideline of the National Heart, Lung, and Blood Institute [86] defines a normal blood pressure in children and adolescents as systolic and diastolic levels below the 90th percentile, according to sex, age and height, and hypertension as systolic or diastolic levels above the 95th percentile. The German Working Group on Pediatric Hypertension developed similarly stratified reference tables from ambulatory blood pressure recordings in 949 healthy children and adolescents from 5 to 20 years old [87]. Stergiou and coworkers [45] recently published comparable reference tables for the self-measured blood pressure in 778 healthy youngsters (age range, 6–18 years) enrolled in the Arsakeion School study. Self-monitoring of blood pressure in children and adolescents, although potentially useful in the follow-up of young patients [43,44], should not be used for the diagnosis of hypertension. The amount by which, even in normotensive youngsters, the self-measured blood pressure is lower than the office and daytime blood pressures needs further clarification[42]. Only few studies documented the
cross-sectional association in youngsters between early signs of target organ damage and the home blood pressure. Finally, no study evaluated to what extent the self-measured blood pressure in children and adolescents predicts transition to hypertension or the risk of cardiovascular complications in young adults or later in life.

**Evidence from clinical trials**

Two clinical trials compared antihypertensive drug treatment guided by the self-measured blood pressure as opposed to office blood pressure: the Treatment of hypertension based on Home or Office blood Pressure (THOP) trial [46] and the Home versus Office blood pressure measurements: Reduction of unnecessary treatment Study (HOMERUS [88]). The Hypertension Objective treatment based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study [48] is still ongoing [89].

**Treatment of hypertension based on Home or Office blood Pressure**

In the THOP trial [46], antihypertensive drug treatment was adjusted in a stepwise manner based on either the self-measured diastolic blood pressure at home (average of six measurements per day during 1 week; 203 patients) or the average of three sitting diastolic readings at the doctor’s office (197 patients). If the diastolic blood pressure guiding treatment was above (>89 mmHg), at (80–89 mmHg) or below (<80 mmHg) target, one physician-blinded to the patients’ randomization intensified antihypertensive treatment, left it unchanged or reduced it, respectively.

The target blood pressure was the same in the two treatment groups. At the end of the study (median follow-up, 350 days; 5th–95th percentile interval, 153–586 days), more patients randomized to self-measurement had stopped antihypertensive drug treatment (25.6 vs. 11.3%; P<0.001) with no significant difference in the proportions of patients progressing to multiple-drug treatment (38.7 vs. 45.1%; P=0.14). The final office, home and 24-h ambulatory blood pressures were higher (P<0.001) in patients randomized to self-measurement than in those treated according to the office blood pressure. The baseline-adjusted systolic/diastolic differences between these two groups averaged 6.8/3.5, 4.9/2.9 and 4.9/2.9 mmHg, respectively. Left ventricular mass and reported symptoms were similar in the two groups [46].

The THOP trial [46] confirmed that the cut-off limit for the diastolic blood pressure should be lower on home than office measurement and suggested that one should account for both systolic and diastolic blood pressures to adjust antihypertensive drug treatment.

**Home versus Office blood pressure measurements: Reduction of unnecessary treatment Study.**

In the randomized HOMERUS trial [47,88], the office blood pressure and the self-measured blood pressure guided antihypertensive drug treatment in the control and experimental group, respectively. In contrast to the THOP trial [46], HOMERUS patients randomized to office blood pressure measurement, did not record their blood pressure at home [88]. The patients underwent ambulatory blood pressure monitoring at entry and at closeout. After a standardized treatment schedule, investigators had to reach the target blood pressure levels of 120–139 mmHg systolic and 80–89 mmHg diastolic. This goal was similar in both treatment groups [47]. A blinded physician at the coordinating centre took the treatment decisions. The stated hypothesis [88] was that at the end of the 1-year follow-up period, patients in both groups would have the same blood pressure, at the expense of more medication in the office blood pressure group.
The patients randomized to self-measurement (n=216) used less medication than those (n=214) allocated to office blood pressure measurement (1.47 vs. 2.48 drug steps; P<0.001) with lower costs ($3222 vs. $4420 per 100 patients per month; P<0.001), but without significant differences in systolic and diastolic blood pressures on office measurement (1.6/1.0mmHg; P=0.25/0.20), in changes in left ventricular mass index (– 6.5 vs. − 5.6 g/m²; P=0.72), or in median urinary microalbumin concentration (– 1.7 vs. −1.5mg/24h; P=0.87). Nevertheless, the 24-h ambulatory blood pressure was higher (125.9/77.2 vs. 123.8/76.1mmHg; P<0.05/0.05) in the self-measurement than the office group [47].

**Hypertension Objective treatment based on Measurement by Electrical Devices of Blood Pressure**

The primary objective of the HOMED-BP study is to determine the optimal level of the self-measured blood pressure, to which hypertensive patients should be treated to achieve the best protection against cardiovascular complications [48]. A secondary objective is to investigate which of the newer antihypertensive drug classes (calcium-channel blockers, angiotensin-converting enzyme inhibitors or angiotensin type-1 receptor blockers) is best suited to initiate blood pressure lowering treatment in Japanese [48]. The study has a 2 x 3 factorial randomized open design with blinded end point validation. The study will include 9000 untreated patients with essential hypertension, aged 40–78 years, whose self-measured blood pressure at home is 135/85mmHg or higher. Eligible patients are randomized to one of the two home blood pressure target groups (125–134/80–84 vs. r125/80 mmHg), and to initial treatment with one of the three drug classes [48].

By the end of March 2003, a total of 1086 patients (12.1% of those planned) had been randomized [89]. Among 653 patients who had been followed for more than 6 months, the self-measured blood pressures at randomization averaged 149/89, 150/89 and 149/88mmHg in the calcium-channel blocker, angiotensin-converting enzyme and angiotensin II receptor blocker groups, respectively. After 6 months, these levels had decreased to 134/81, 135/80 and 133/80 mmHg, respectively, with no significant between-group differences. In the intensive and usual treatment groups, the self-measured blood pressures at randomization and at 6 months were 149/88 and 150/89mmHg and 134/80 and 135/80 mmHg, respectively without significant between-group differences. In the less-intensive treatment group, 45% of the 304 patients achieved a systolic blood pressure below 135mmHg, whereas 60% achieved a diastolic blood pressure of less than 85 mmHg. In the intensive treatment group, 22% of the 349 patients achieved a systolic blood pressure below 125 mmHg, and 42% reached a diastolic blood pressure of less than 80 mmHg. These results [89] prove that, even under the standardized conditions of a clinical trial, it is very difficult to control blood pressure and that doctors should at least strive to lower the self-measured blood pressure at home to levels below the commonly accepted [49,50,57,62] therapeutic target of 135/85mmHg. In the Japan Home versus Office blood pressure Measurement Evaluation study, only 34% of 3400 hypertensive patients achieved these levels [90].

**Current guidelines**

We reviewed the diagnostic thresholds for the self-measured blood pressure (Table 4) in the guidelines for the management of hypertension, published in 2000 at the occasion of the first consensus meeting on the self-measured blood pressure [49] or later [50–52,54–62]. Self-monitoring refers to the blood pressure measured at home in all guidelines [49–52,54–62], whereas the American recommendations [56,61] leave the possibility open for self-monitoring at the work place. The results of our review of guidelines are summarized in Table 4.
Proposal for diagnostic and therapeutic thresholds

The association between blood pressure and cardiovascular risk is continuous, without a threshold above which the risk suddenly increases. Clinical decisions, however, must be based on operational thresholds. Worldwide consensus is that the cut-off limits applicable for conventional sphygmomanometry cannot be extrapolated without further validation to the self-measured blood pressure at home, because studies in unselected populations [21–30] and hypertensive patients [32–36] demonstrated that the self-measured blood pressure, compared with the office blood pressure, is lower.

Table 4  Diagnostic thresholds in guidelines for the management of hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Target group</th>
<th>Systolic/diastolic threshold (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First consensus</td>
<td>2000</td>
<td>Adults</td>
<td>≥ 130/85 (HT)</td>
</tr>
<tr>
<td>meeting [49]</td>
<td></td>
<td></td>
<td>≥ 135/85 (D-HT)</td>
</tr>
<tr>
<td>Japanese</td>
<td>2002</td>
<td>≥ 65 years</td>
<td>&lt;125/80 (NT)</td>
</tr>
<tr>
<td>elderly [50]</td>
<td></td>
<td></td>
<td>≥ 135/85 (HT)</td>
</tr>
<tr>
<td>JSH [51]</td>
<td>2003</td>
<td>Adults</td>
<td>&lt;125/75 (D-NT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;125/80 (NT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 135/80 (HT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 135/85 (D-HT)</td>
</tr>
<tr>
<td>ESH [52]</td>
<td>2003</td>
<td>Adults</td>
<td>≥ 135/85 (HT)</td>
</tr>
<tr>
<td>WHO/ISH [54]</td>
<td>2003</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>US Task Force [55]</td>
<td>2003</td>
<td>Adults</td>
<td>...</td>
</tr>
<tr>
<td>JNC7 [56]</td>
<td>2003</td>
<td></td>
<td>&lt;130/80 (NT)</td>
</tr>
<tr>
<td>ESH Working Group [57]</td>
<td>2004</td>
<td>Adults</td>
<td>&lt;130/80 (NT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 135/85 (HT)</td>
</tr>
<tr>
<td>BHS [58]</td>
<td>2004</td>
<td>Adults</td>
<td>&lt;130/80 (NT)</td>
</tr>
<tr>
<td>CHEP [59]</td>
<td>2004</td>
<td>Adults</td>
<td>&gt;136/83 (HT)</td>
</tr>
<tr>
<td>ESH [60]</td>
<td>2005</td>
<td>Adults</td>
<td>&lt;130/80 (NT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 135/80 (HT)</td>
</tr>
<tr>
<td>AHA [61]</td>
<td>2006</td>
<td>Adults</td>
<td>&lt;130/80 (NT)</td>
</tr>
<tr>
<td>BJS [62]</td>
<td>2006</td>
<td>Adults</td>
<td>&gt;135/85 (HT)</td>
</tr>
</tbody>
</table>

An ellipsis indicates that the guideline did not provide any concrete recommendation.

AHA, American Heart Association; BJS, British Joint Societies; CHEP, Canadian Hypertension Education Program; D-NT, definite normotension; ESH, European Society of Hypertension; HT, hypertension; ISH, International Society of Hypertension; JNC7, Joint National Committee, version 7; JSH, Japanese Society of Hypertension; NT, normotension.

Proposal for diagnostic and therapeutic thresholds

The association between blood pressure and cardiovascular risk is continuous, without a threshold above which the risk suddenly increases. Clinical decisions, however, must be based on operational thresholds. Worldwide consensus is that the cut-off limits applicable for conventional sphygmomanometry cannot be extrapolated without further validation to the self-measured blood pressure at home, because studies in unselected populations [21–30] and hypertensive patients [32–36] demonstrated that the self-measured blood pressure, compared with the office blood pressure, is lower.
Diagnostic thresholds
Definition of normality for the self-measured blood pressure at home is following the same path as that for defining normality of the ambulatory blood pressure [91,92]. The first reference values for the self-measured blood pressure started from its distributional characteristics in participants with a normal office blood pressure [19,20]. Subsequent cross-sectional studies demonstrated stronger association of target-organ damage with the self-measured than with the office blood pressure. It, however, took over 20 years to collect the necessary prospective data (Table 3) to define normality in terms of cardiovascular risk [21–23,29,30,32–36].

Table 5 shows an updated proposal for diagnostic thresholds for the self-measured blood pressure at home. Two meta-analyses [19,20], prospective studies in populations [21–30], hypertensive patients [32–36] and pregnant women [37,38], as well as the consensus in current guidelines (Table 4, [49–54,56–62]) support the idea that hypertension on self-monitoring at home starts at blood pressure levels of 135mmHg systolic or 85mmHg diastolic.

Table 5  Updated proposals for thresholds

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Optimal (mmHg)</th>
<th>Normal (mmHg)</th>
<th>Hypertension (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>&lt;120/80</td>
<td>&lt;130/85</td>
<td>≥ 140/90</td>
</tr>
<tr>
<td>Daytime ambulatory</td>
<td>&lt;120/80</td>
<td>&lt;130/85</td>
<td>≥ 135/85</td>
</tr>
<tr>
<td>Self-measured (home)</td>
<td>&lt;120/80</td>
<td>&lt;130/85</td>
<td>≥ 135/85</td>
</tr>
</tbody>
</table>

For evidence in support of the thresholds, see text.

The evidence for optimal and normal blood pressure levels on self-measurement is much weaker. In the Kahoku study [33], men with systolic levels from 125 to 134mmHg were at the lowest risk of death. International databases of individual-patient data demonstrated that the difference between automated [20,91] and conventional blood pressure readings increases with the level of the office blood pressure. In participants with normotension on office blood pressure measurement, the mean differences between the office and self-measured blood pressures (116.9/72.8 vs. 115.4/70.7mmHg [20]) and between the office and the daytime ambulatory blood pressures (119/73 vs. 122/75mmHg [91]) were only 1.5/2.1 [20] and 3.0/2.0mmHg [91], respectively. Recent analyses found that levels of 120/80 and 130/85mmHg carried similar 10-year cardiovascular risks on both office and daytime ambulatory measurement [93]. Until more prospective data become available, it seems reasonable to propose values below 120/80mmHg and below 130/85mmHg as optimal and normal, respectively, also for the self-measured blood pressure at home.

Current diagnostic thresholds for the conventionally measured office blood pressure and ambulatory blood pressure are applicable irrespective of sex and age. In line with the recommendation of the 2000 consensus meeting [49], the thresholds in Table 5 might be used for adult as well as older patients and for women and men alike.
Therapeutic thresholds

The target levels of the self-measured blood pressure to be attained on antihypertensive drug treatment are currently unknown. The HOMED-BP study is still ongoing [89]. Therapeutic targets for the home blood pressure (<135/85 mmHg), however, should logically be lower than those used to diagnose hypertension (≥135/85 mmHg). As for the office blood pressure [53], lower treatment targets might be advisable in high-risk patients, such as those with diabetes mellitus, a history of stroke, coronary heart disease or renal dysfunction. Direct evidence, however, supporting these lower targets is not yet available. The Japanese experience [89] shows how difficult it is even under the best possible conditions to lower the self-measured blood pressure to less than 135mmHg systolic and 85mmHg diastolic.

Two considerations might be helpful in titrating antihypertensive drug treatment according to the self-measured blood pressure. First, in keeping with large-scale prospective observational studies [94,95], metaregression analyses published by us [96–98] and other research consortia [99–101] demonstrated that small gradients in the achieved systolic office blood pressure explained most of the differences in the cardiovascular outcomes, as observed in randomized clinical trials. This association was particularly strong for the prevention of stroke [99], the complication most directly associated with blood pressure [102] and weakest for heart failure [99]. Any reduction in the systolic conventional blood pressure by 3 mmHg will reduce the incidence of stroke, myocardial infarction and cardiovascular events by approximately 20, 15 and 15%, respectively[103]. Any reduction in the conventional blood pressure will also be accompanied by a decrease in the self-measured blood pressure at home. As already shown for the daytime ambulatory blood pressure in the Systolic Hypertension in Europe trial (systolic daytime vs. office, 9.3 vs. 16.6 mmHg; diastolic, 4.9 vs. 7.3mmHg; systolic/diastolic daytime-to-office ratio, 0.59/0.67) [104], estimates of the treatment induced blood pressure lowering effects are smaller on automated than office measurement. In the Ambulatory blood Pressure monitoring and Treatment of Hypertension trial [105], this ratio was 0.64 systolic (14.3 vs. 22.4mmHg) and 0.70 diastolic (9.5 vs. 13.7mmHg). In the THOP trial [46], the home-to-office ratios in the blood pressure lowering effect were 0.73 systolic (13.5 vs. 18.6mmHg) and 0.71 diastolic (8.7 vs. 12.2mmHg). These findings suggest that relative risk reductions might be approximately equivalent for any decrease in the systolic blood pressure by 2mmHg at home or by 3mmHg at the office.

Second, in the light of the low control rates in the HOMED-BP trial [89], absolute benefit might override the importance of lower therapeutic goals in high-risk compared with normal-risk patients. As suggested above, one might assume that lowering the home systolic blood pressure by 2mmHg would result in a 20% reduction in the incidence of stroke, independent of the risk at baseline. At a rate of 35.9 strokes per 1000 person-years (Fig. 3, [27]) lowering systolic blood pressure at home by a mere 2mmHg in 1000 patients for 1 year would approximately prevent seven strokes. At a rate of 6.9 strokes per 1000 person-years (Fig. 3, [27]), the corresponding estimate would be only one stroke.

Rather than underscoring the importance of lower therapeutic thresholds in high-risk patients, it might be more encouraging to highlight that each millimetre of mercury counts in the prevention of cardiovascular complications by blood pressure lowering treatment and that absolute benefit and therefore the number to treat is proportional to the absolute risk. Nevertheless, even if every millimetres of mercury counts in prevention, opinion leaders should convince physicians to adopt a more aggressive approach in the control of blood pressure, irrespective of the way it is measured.
Conclusion
The thresholds to diagnose hypertension from the self-measured blood pressure at home remain basically unaltered since the 2000 consensus conference [49], but they are currently supported by evidence from prospective outcome data in populations [21–30] and patients [32–36]. Moreover, two recently published studies [106,107] proved that the introduction of the self-measured blood pressure in the management of hypertensive patients reduces medical costs. In contrast, further studies must establish what values of the self-measured blood pressure are optimal and normal in terms of cardiovascular outcome.

Acknowledgement
Gianfranco Parati, Grzegorz Bilo, Giuseppe Mancia (University of Milano-Bicocca, Milan, Italy), Roland Asmar (L’Institut Cardiovasculaire, Paris, France) and George Stergiou (Third University, Athens, Greece) organized the Consensus Conference on Blood Pressure Self-Monitoring at Home (Milan-Verbania, 13–14 June 2007; http://www.aimgroup.it). The authors gratefully acknowledge the expert assistance of Sandra Covens and Ya Zhu in maintaining the Reference Manager database.

Conflict of interest: none declared.
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Part 2

Progression of blood pressure measurement

Chapter 3.2

The physician and the hospital separately and independently influence blood pressure.

Ahmet Adiyaman
Ismail Aksoy
Dirk G. Dechering
Jaap Deinum
Jan A. Staessen
Theo Thien

Submitted.
Abstract

**Objective** To determine the separate contribution of the physician and the hospital environment to differences between home and office blood pressure (BP).

**Methods** For 3 consecutive days 65 hypertensive patients measured their blood pressure at home (HBP). Office BP (OBP) was determined with the same device by the physician. A higher or lower OBP than HBP was regarded white coat effect (WCE) or masked effect (ME) respectively. OBP was measured automatically before, during and after the presence of the physician. The physician’s effect (PE) was the BP rise caused by the entrance of physician. The WCE or ME minus the PE was regarded the hospital’s contribution to the BP differences (HE). A pronounced WCE, ME and PE was regarded a >10 mmHg systolic or >5 mmHg diastolic difference.

**Results** A pronounced WCE was present in 20% of (13/65) the patients (mean SBP/DBP ± SD 11.1/7.4 ± 10.9/5.2 mm Hg). The hospital environment contributed more to the WCE (6.9/4.9 ± 10.9/5.3 mmHg) than the PE (4.1/2.6 ± 5.3/2.5 mmHg). A pronounced ME was present in 53.5% (n=35) of participants (mean 17.0/9.8 ± 12.7/8.3 mmHg). The BP difference induced by the hospital environment (-21.4/-13.1 ± 14.0/9.7 mmHg) was larger (P<0.001) than the physician induced BP difference (4.3/3.3 ± 6.2/4.1 mmHg). WCE or ME did not correlate with the PE.

**Conclusions** BP differences between home and office can largely be attributed to the hospital environment rather than to the physician. The physician related BP effect is not related to the WCE or to the ME.
**Introduction**

In 1983 Mancia and colleagues were the first reporting an immediate blood pressure (BP) increase when a physician entered the room to start a BP reading[1]. This phenomenon was labelled as the white coat effect (WCE). The term white coat hypertension (WCH) was introduced[2], in case the BP was only hypertensive in the presence of physician but normotensive in the absence. With the entrance of automatic devices for BP measurement outside the clinic environment at home (HBP) or in ambulatory BP monitoring (ABPM), office hypertensives with home normotension were additionally labelled WCH, in assumption that the higher BP in the office was caused solely by the physician[3]. In this context, treated hypertensives with higher BP in the office than at home were also regarded as having WCE. Although both labelled the same, office-home differences in BP are not similar to BP differences in the office induced by the entrance of the physician. More recently, the term masked hypertension (MH) was introduced for office normotensives with hypertension at home[4]. In analogy with WCH and WCE the term masked effect (ME) is now customary for higher BP values at home than in the office in treated hypertensives.

It is known that the hospital environment in itself may induce a stress reaction and that the entrance of the physician induces a second stress upon the first. In the intra-arterially study of Mancia, the entrance of the physician is the only stress whereas in most non-invasive studies the sum of both hospital and physician stress is used, without knowledge about the separate contribution of the two stress producers[1]. In a few studies looking for the relation between the pure physician induced BP increase and the difference between the office BP and daytime ABPM, the authors concluded that such a relation was not found[5-7]. As the specific contribution of the hospital environment on BP differences between home an office was never investigated before, the aim of our present study was to investigate the separate contributions of both the hospital environment and entrance of a physician to the WCE. We also investigated the association of stress by the hospital environment with stress caused by the physician. In order to differentiate between the different phenomena, we will use the term physician effect (PE) for the pure effect on BP by the physician, we will use WCE for higher BP in the office than at home, and we will use hospital effect (HE) for the separate contribution of the hospital environment on the WCE. Figure 1 shows how the different phenomena are related to each other.

**Figure 1.** Schematic representation of the different blood pressure phenomena.
**Methods**

**Patients**
Participants were patients visiting the outpatient clinic of a university hospital routinely (mostly treated hypertensives). Exclusion criteria were: diabetes mellitus, cardiac arrhythmias, heart failure and autonomic insufficiency. Participants were informed and asked for informed consent. They were trained by the male physician (I.A.) to perform semi-automatic BP-measurement at home and were educated to prevent factors influencing correct BP-measurement (smoking, talking, exercise etc.).

**Blood pressure measurement**
Upper arm circumferences were measured and appropriate cuffs were used. All participants measured their home BP with a validated semi-automatic oscillometric device, the Omron 705CP (Omron Healthcare Europe B.V., Hoofddorp, The Netherlands)[8]. Triple measurements were made at the non-dominant arm after at least 5 min of rest, every morning and evening for 4 consecutive days, sitting in a comfortable chair with the back supported, feet flat on the floor and the arm at heart level[9, 10]. The BP values were noted by the patients, and the values were checked by the physician from the device memory to confirm the validity. One day after the last home BP-readings, their BP was measured in the office. Participants were comfortably seated on a seat with arms on a support at heart level and were not allowed to perform activities influencing BP[11]. BP-readings were performed with both the Omron device at the non-dominant arm, and a fully automated oscillometric BP-measuring device (Dinamap 1846SX, Critikon, Tampa, Florida) on the contralateral arm. The Dinamap was programmed to perform one BP reading automatically at 8 min, without the presence of a physician. After this, at exactly t=10 min, the physician (always the same male physician, especially trained for the study, I.A.) entered and performed two bilateral BP-readings with both the Dinamap and the Omron device simultaneously[8]. All participants were familiar to the physician as they were previously carefully instructed by him about the measurements. After the two simultaneous measurements with both the Omron and Dinamap device, the physician left the room (at about t=12 minutes). At t=15 min the Dinamap again performed an automatic measurement, in the absence of the physician. No changes in antihypertensive treatment were made during the study period.

**Data and statistical analysis**
The home measurements of the first day were excluded. The mean of all remaining home BP readings was regarded as the HBP. The mean of the two BP-readings performed by the physician with the same device at t=10-12 min, was regarded as the OBP. The difference between office and home BP (determined by the Omron device) was regarded the WCE or ME. The mean of the BP-readings at t=10-12 min, in presence of the physician, minus the mean of the BP-readings at t=8 and 15 min, without the physician was regarded the PE. The contribution of the hospital environment to the BP differences was calculated (HE = WCE – PE or HE = ME – PE). The ME was defined as a higher self measure BP at home than the BP measured with the same device by the physician in the office. A >10mmHg systolic BP or >5 mmHg diastolic BP higher or lower OBP than HBP was regarded as a pronounced WCE or ME respectively. A >10 mmHg systolic BP or >5 mmHg diastolic BP higher BP in the presence than the absence of the physician was regarded a pronounced PE. Magnitudes of HE and PE were calculated both for all participants with WCE and for participants with a pronounced WCE. The same was done for patients with ME and for patients with a pronounced ME. Differences between WCE or ME and PE were tested for significance by means of the Student’s t-test. Pearson’s correlation coefficients were calculated to assess the
association between PE and WCE or ME. We determined linear regression coefficients when assessing the relation of age, sex, BMI and baseline mean BP for the different BP phenomena. Significance was set throughout the article at a $P$-value of $<0.05$ (two-sided).

**Results**

**Patient characteristics**
Our study consisted of 65 patients (33 females) of whom 57 were treated. All patients were familiar with the hospital environment, as they were regularly followed up for hypertension, vascular or metabolic disease. Mean age ± SD was 59 ± 14 years (ranging from 29-86). Mean height was 172 ± 10 cm. Mean body mass index was 27.6 ± 4.6 kg/m$^2$. Table 1 shows the baseline characteristics for patients with systolic WCE (n=20) or ME (n=45). No significant differences were present in age, height, weight or body mass index.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of participants with systolic white coat effect or masked effect.</th>
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<tbody>
<tr>
<td>Females (%)</td>
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<tr>
<td>Age (years)</td>
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<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Body mass index (kg/m$^2$)</td>
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<tr>
<td>OBP–HBP (Omron)</td>
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<tr>
<td>Δ BP by physician (Dinamap)</td>
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<tr>
<td>Δ BP by hospital (calculated)</td>
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</table>

All values were rounded to whole units. Data are number (%) or mean (± SD). Blood pressures are presented as systolic blood pressure/diastolic blood pressure/pulse rate ± SD. N.s., not significant; OBP, office blood pressure; HBP, home blood pressure; Omron/Dinamap, device used;.

**Blood pressure differences in the whole group**
While there were significant differences in HE between patients with WCE and ME, no significant differences in the magnitude of the PE were present. Table 2 shows the BP values at baseline for the total group and by gender. No significant differences in BP ($P > 0.4$) were present between the office measurements at t=8 (mean 136.1/77.8 mmHg) compared to t=15 minutes (135.3/77.5 mmHg). This justified us to use the mean BP of t=8 and t=14 as the office BP without the presence of the physician. We omitted all home BP measurements of the first day. This however did not make a difference (144.2/83.1 mmHg, 64.8 bpm vs. 144.2/83.2 mmHg, 65.0 bpm, $P$-values for the differences in SBP, DBP and PR $>$0.85). Surprisingly, mean HBP was higher than the mean OBP ($P$<0.001 for SBP and DBP). Figure 2 shows the mean and individual BP effects for the whole group.

<table>
<thead>
<tr>
<th>Table 2. Mean blood pressures, pulse rates and blood pressure effects.</th>
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<tbody>
<tr>
<td>Females (%)</td>
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<td>Age (years)</td>
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<td>OBP (Omron, dr.)</td>
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<td>HBP (Omron)</td>
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<td>OBP (Dinamap)</td>
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<td>OBP (Dinamap, dr.)</td>
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<td>OBP–HBP (Omron)</td>
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<tr>
<td>(Dinamap)</td>
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<tr>
<td>Δ BP by hospital</td>
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</tbody>
</table>

All values were rounded to whole units. Data are presented as systolic blood pressure/diastolic blood pressure/pulse rate ± SD. Omron/Dinamap, device used; dr., physician present; OBP, office blood pressure; HBP, home blood pressure.

**Figure 2.** Blood pressure effects in all participants. The rectangles in the upper part of the figure resemble the patients with a relevant white coat effect (n=13) depicted in figure 3. The white coat effect is divided into a physician effect and a hospital effect. Data is presented as mean with 95% CI. SBP, systolic blood pressure; DBP, diastolic blood pressure; WCE, white coat effect; PE, physician effect; HE, hospital effect.
The white coat effect
The mean WCE in 20 patients with higher OBP than HBP was 9.0/1.7 ± 8.2/10.2 mmHg. No significant effect on pulse rate was present (mean 0.9 ± 6.8 bpm). A significantly higher WCE was present in women than in men (13.0/-0.7 ± 9.9/13.2 mmHg vs. 5.7/3.6 ± 4.8/6.9 mmHg). The WCE consisted of 4.6/-1.7 ± 9.9/10.9 mmHg HE and of 4.4/3.4 ± 6.6/3.3 mmHg PE. PE did not correlate with WCE (r=0.12, P=0.61 for SBP and r=-0.05, P=0.83 for DBP).

A substantial WCE (SBP >10 or DBP >5 mmHg higher OBP than HBP) was present in 13 of the 65 (20%) participants. The mean WCE in these 13 participants was (SBP/DBP ± SD) 11.1/7.4 ± 10.9/5.2 mmHg (Figure 3).

Figure 3. Blood pressure effects in patients with a relevant white coat effect (n=13). The white coat effect is divided into a physician effect and a hospital effect. Data is presented as mean with standard error of the mean. SBP, systolic blood pressure; DBP, diastolic blood pressure; WCE, white coat effect; PE, physician effect; HE, hospital effect.

No significant effect on pulse rate was present (mean 0.8 ± 7.0 bpm). Of this effect 4.1/2.6 ± 5.3/2.5 mmHg was due to the physician and 6.9/4.9 ± 10.9/5.3 mmHg due to the hospital environment. In regression analysis, age, baseline mean arterial pressure (at home) and BMI were not significantly associated with a significant WCE (all P-values >0.4). Also within this subgroup of patients with a substantial WCE, significantly higher systolic WCE (P=0.009) was present in women (20.2/7.7 ± 7.0/6.4 mm Hg) compared to men (5.4/7.3 ± 8.9/4.8 mmHg), while they did not differ in change of pulse rate (P=0.69). Baseline mean arterial pressure or age did not significantly influence the systolic or diastolic WCE (all P-values >0.175). The difference between the PEf and the WCE was significant for both SBP (P=0.04)
and DBP ($P=0.006$). PE correlated poorly with WCE ($r=0.24$, $P=0.43$ for SBP and $r=0.22$, $P=0.47$ for DBP).

**Masked effect**
The mean ME in 45 patients with higher HBP than OBP was $15.1/6.4 \pm 11.5/8.1$ mmHg. No significant effect on pulse rate was present (mean $-0.1 \pm 5.8$ bpm). No significant differences were present in ME, HE or PE between these 21 men and 24 women. The ME consisted of a substantially larger HE ($19.6/9.4 \pm 12.7/9.5$ mmHg) than PE ($4.6/3.0 \pm 6.4/3.9$ mmHg). PE did not correlate with ME ($r=0.08$, $P=0.59$ for SBP and $r=-0.13$, $P=0.39$ for DBP).

A substantial ME (SBP >10 or DBP >5 mmHg higher HBP than OBP) was present in 35 of 65 participants (53.5%), with a mean effect of $17.0/9.8 \pm 12.7/8.3$ mmHg and $-1.1 \pm 6.2$ bpm (Figure 4).

**Figure 4.** Blood pressure effects in patients with a relevant masked effect ($n=35$). The masked effect is divided into a physician effect and a hospital effect. Data is presented as mean with standard error of the mean. SBP, systolic blood pressure; DBP, diastolic blood pressure; ME, white coat effect; PE, physician effect; HE, hospital effect.

Also in these patients, the magnitude of the BP difference induced by the hospital environment ($-21.4/-13.1 \pm 14.0/9.7$ mmHg) was larger ($P<0.001$) than the physician induced BP difference ($4.3/3.3 \pm 6.2/4.1$ mmHg). In multivariable regression analysis, age significantly increased the ME ($\beta=0.372$, $P=0.045$). Sex, baseline mean arterial pressure and BMI did not have significant influence on the systolic ME ($P \geq 0.15$). Age ($\beta=0.286$, $P=0.10$) and baseline mean arterial pressure ($\beta=0.317$, $P=0.07$) were borderline significantly associated with the diastolic ME. The systolic and diastolic ME did not correlate with influence of the physician on BP (all $P$-values $>0.4$).
The physician effect
A significantly higher rise of BP due to the physician was present in women (6.1/4.0 mmHg ± 5.9/4.3, \(P=0.04\) for SBP and DBP) than in men (2.8/2.2 mmHg ± 6.5/2.7). BP was 4.5/3.1 mmHg ± 6.4/3.7 higher in the presence versus the absence of the physician in the hospital (\(P<0.001\) for SBP and DBP), while pulse rate (-0.2 ± 7.0 bpm) was not altered (\(P=0.81\)).

A substantial PE (SBP >10 or DBP >5 mmHg rise) was present in 30 (46%) of 65 participants. Significantly more women (n=20) than men (n=10) had a PE (\(P=0.03\)). The mean PE in these 30 subjects amounted to 7.8/5.8 mmHg ± 6.6/3.1 and -2.1 ± 7.2 bpm. In this group, sex, age, baseline mean arterial pressure or BMI, did not significantly influence the systolic or diastolic PE (all \(P\)-values >0.25).

Of the 30 subjects with a substantial PE, only 4 (13%) had a substantial WCE, assessed by difference of home and office BP. This was because of the presence of a higher BP at home than in the hospital in the absence of the physician (–19.5/–13.7 ± 14.8/9.1 mmHg and 3.1 ± 8.9 bpm) in 24 persons. This eventually resulted in a mean ME of 8.0/5.9 ± 16.7/10.0 mmHg and 1.4 ± 6.6 bpm. In 60% (18 of 30) of the participants with a substantial ME, also a substantial PE (mean 6.5/5.5 ± 6.4/3.8 mmHg and -2.9 ± 8.4 bpm) was present.

Discussion
In participants with a substantial WCE (20%), this WCE could largely be attributed to the hospital environment rather than to the presence of a physician. Even in patients with a substantial PE, often no substantial WCE, determined by office-home BP difference, was present. This was mostly due to the presence of a large ME. PE and the WCE or ME did not correlate with each other. The HE and the PE therefore, seem to be two different entities determining the WCE or the ME.

Previous research showed that PE and WCE did not correlate well[6, 7]. Our study was confirmatory in this matter. These two phenomena should therefore be regarded as different entities, with possibly a different etiology. The PE could be caused by a stress reaction caused by the entrance of a physician, resulting in sympathetically mediated vasoconstriction and rise in blood pressure[12]. A significant rise of pulse rate observed in beat-to-beat monitoring in the acute moment of entrance of the physician, supports sympathetic activity as being the cause of the effect[13]. Moreover, plasma cortisol levels were higher in subjects with, compared to those without a PE[14]. In our current study, no significant rise in pulse rate was observed in our present investigation. The full automatic Dinamap measured BP and pulse rate about one minute after entrance of the physician. Due to this slight delay we could not measure the acute situation, where besides BP, possibly, pulse rate rises[1]. We might have measured the pulse rate at a time in which the baroreceptor reflex has already downregulated the heart rate. The lack of a rise in pulse rate in the surrogate marker of WCE, defined as difference between OBP and HBP or ABPM, has been described in previous literature[6, 15, 16]. We confirmed this lack of change in pulse rate in WCE assessed by office-home BP differences.

We hypothesize that besides the role of physician, other factors like BP variability, differences in medication (difference in pharmacokinetics of the antihypertensive drugs used), difference between methods (different devices, environment and time of measurement) and difference in behavior of patients during home measurements (activity/exercise, smoking and diet) are important causes of the difference in BP observed between home and office. The sum of these factors has been previously named ‘an idiosyncratic reaction to the hospital
environment[13]. In our present study we have gathered all these potential factors into the HE. The question if sympathetic autonomic activity has a greater role in the PE than in the ‘surrogate’ WCE should be investigated further. Table 3 shows an outline of previously published articles about the (lack of) association of the classic WCE (named PE in our study) and the surrogate WCE.

To the best of our knowledge, we are the first to specifically investigate the role of the hospital environment in differences of BP between home and office. Previously, Gerin and colleagues successfully studied the extent to which different clinical settings influence BP before seeing a physician [15]. In that study different measures in the clinic (BP in the waiting room, examination room with and without physician) were compared to a ‘non clinical’ hospital setting and daytime ABPM. They concluded that WCE may not be just limited to the narrow window in which the patient sees the physician, but may be generalized to the clinical setting. In an accompanying editorial[17], Parati and Mancia claimed that any improvement in methods for measuring blood pressure in the clinic (for instance, in the absence of a physician) was unlikely to remove the confounding influence of the WCE on blood pressure measurements. The latter statement should be assessed with care though. More recent studies of Myers and colleagues provided consistent evidence that automated BP measurement in the office in the absence of a physician correlated strongly with and were similar to daytime ABPM values[18]. However, evidence that the automated BP measurement in the office in absence of the physician predicts cardiovascular morbidity and mortality as good as daytime ABPM are to be awaited.

Stergiou and colleagues studied different home and clinic measurements in order to assess the correct term for home measurement[19]. They concluded that it did not matter whether home measurements were made by patients or relatives, and by patients or the physician in the hospital. The BP measured by the physician in the hospital was only slightly higher (1.9/1.6 ± 6.1/4.7 mmHg) than measured by the patient 5 minutes after the physician left. The difference of self-measured BP in the office versus self-measured BP at home was much larger (9.3/4.9 ± 9.0/5.4 mmHg). This underscores our conclusion, namely that the hospital setting has a more important influence in home-office BP differences, than the presence of the physician. In this line, ‘isolated office hypertension’ seems to be a more correct term than white coat hypertension, when the data is based on home-office BP difference.

In our study, remarkably, mean OBP was lower than mean HBP, despite excluding HBP readings of the first day. Other studies showed similar results[15, 20]. Firstly, we can hypothesize that the cause could be an insufficient resting period before the self measurement, despite the fact that we advised 10 minutes of rest before self-measurement. In contrast, during OBP measurement, the physician secured at least 10 minutes of rest before taking a BP-reading. Secondly, the cause could be an alerting reaction or stress caused by the self measurement at home. Finally, the possibility exists of an occasional large group of persons with ME in our population, because of selection of patients who regularly visited the hospital. Moreover, all patients were seen by only one well-trained physician.

Our study is one of very few, assessing blood pressure differences, using the same device for home and office measurements. In previous studies regarding BP differences between home and the office, different BP measurement techniques (mercury or aneroid sphygmomanometer in the office vs. ambulatory or fully automated oscillometric devices at home) were used. Comparison of cut-off values between different measurement techniques are often based on percentiles in population studies. If this comparison could be made on an individual basis for
the screening of WCE or ME is questionable. We made use of identical devices for evaluation of the PE (all measurements with Dinamap) or the WCE (all measurements with Omron).

**Perspectives**
The term WCE is thus largely used for two different phenomena; difference in BP between office and home, and BP difference caused by the entrance of the physician (or nurse). Our findings show that WCE and PE have only a weak correlation, and can be in the opposite direction. We are the first that specifically studied the separate impacts of both the hospital environment and the presence of the physician on BP. We concluded that the hospital environment is the largest factor that influences BP differences between home and office BP (e.g. WCE and ME).

**Disclosures**
None.
Table 3. Previous literature regarding (dis)agreement between the true WCE and the ‘surrogate’ WCE.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Population</th>
<th>Method</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Parati et al.[6]</td>
<td>28 hypertensives</td>
<td>Finger BP recorded before and during the visit of the physician</td>
<td>No relation between physician-dependent peak BP increase and office-daytime ABPM-difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BP measured during visit with mercury sphygmomanometer was compared to daytime ABPM</td>
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<tr>
<td>Lantelme et al.[7]</td>
<td>88 hypertensives</td>
<td>Classic WCE determined by finger BP</td>
<td>The estimated WCE relates poorly to the classic WCE</td>
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<td>• The surrogate WCE was assessed by difference between office BP (by a physician) and 24-hour ABPM</td>
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<td>Palatini et al.[5]</td>
<td>64 hypertensives</td>
<td>Responses to BP measurement by a physician were assessed with beat-to-beat finger BP recording</td>
<td>The surrogate WCE was unrelated to the BP response in the office by the physician</td>
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<td>and 33 normotensives</td>
<td>• Difference between office BP and daytime ABPM was used as a surrogate measure of WCE</td>
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ABPM, ambulatory blood pressure monitoring; BP, blood pressure; WCE, white coat effect.
References


Part 3

Procession of blood pressure: The Ambulatory Arterial Stiffness Index

Chapter 4.1

The Ambulatory Arterial Stiffness Index; a novel indicator of cardiovascular risk.

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Submitted.
Abstract — In March 2006, a consortium of researchers introduced a new marker of arterial stiffness, the ‘Ambulatory Arterial Stiffness Index’ (AASI). AASI was defined as unity minus the regression slope of diastolic blood pressure on systolic blood pressure in 24-hour ambulatory blood pressure recordings. The stiffer the arterial tree, the closer the regression slope is to 0 and the AASI is to 1. AASI has proven to predict total cardiovascular mortality, fatal and non-fatal stroke and target organ damage, over and beyond classical risk factors. This review highlights and discusses (a) the physiologic principles of the AASI, its determinants and association with other markers of arterial stiffness (b) cross-sectional studies focusing on the relationship of AASI with hypertensive target organ damage (c) prospective studies in which AASI predicted cardiovascular morbidity and mortality. Finally we summarized perspectives and future challenges regarding the AASI.
Introduction
Cardiovascular disease is the major cause of morbidity and mortality in the ageing populations of the world in developing and developed regions alike. Scientists and policy makers increasingly recognize the role of prevention, which is the continuum of knowledge of the cause, subsequently coming to a diagnosis, and finally initiating treatment. Arterial stiffness is a marker of arterial ageing and predicts future cardiovascular morbidity and mortality over and beyond traditional risk factors[1-4]. It is an appealing measure as it can be determined automatically and non-invasively.

In march 2006, a consortium of researchers introduced a new indirect marker of arterial stiffness, the Ambulatory Arterial Stiffness Index (AASI)[5]. This method is based on physiological insights, already reviewed in 1914[6]. In elastic arteries any increase in systolic blood pressure (SBP) will be accompanied by a similar rise in diastolic blood pressure (DBP), whereas in stiff arteries, DBP will increase less or even fall with higher SBP. AASI was therefore defined as 1 minus the regression slope (Figure 1) of DBP on SBP in 24 hour ambulatory blood pressure recordings (ABPM).[7] The regression line was not forced through the origin, because during diastole when flow drops to zero, such a phenomenon does not occur for blood pressure[8]. The stiffer the arterial tree, the closer the regression slope to 0 and AASI to 1, respectively. AASI can be easily computed from ordinary 24 hour ABPM and therefore does not necessitate any extra equipment or observer training.

Figure 1. Derivation of the ambulatory arterial stiffness index (AASI) from a 24-hour ambulatory blood pressure recording in one participant, whose 24-hour blood pressure was 129 mm Hg for systolic blood pressure and 95 mm Hg for diastolic blood pressure.
This review of the recent literature highlights (a) the physiologic principles of the AASI, its determinants and association with other markers of arterial stiffness (b) cross-sectional studies focusing on the relationship of AASI with hypertensive target organ damage (c) prospective studies in which AASI predicted cardiovascular morbidity and mortality. Finally, we will summarize perspectives and future challenges regarding this promising new marker of arterial stiffness.

Comparison with other markers of arterial stiffness

Markers of arterial stiffness include aortic pulse wave velocity (PWV) and the augmentation Index (AIx). At a constant resting blood pressure level PWV reflects stiffness of the arterial wall because blood flow is faster in a more rigid than in an elastic artery. AIx rests on the principle that in stiffer arteries reflected waves travel faster and augment SBP. Both measures of arterial stiffness predict cardiovascular disease[9, 10]. These techniques however require the use of expensive devices and the involvement of highly trained observers, which renders them unsuitable for use in routine clinical practice. Moreover they should be performed apart from the standard screening procedure of the Framingham or SCORE risk models, whereas AASI could be determined from a 24-h ABPM[11, 12]. The QKD (QRS to Korotkoff Delay) interval is derived from the time between the QRS-wave on the electrocardiogram and the detection of the last Korotkoff sound during deflation of the cuff in 24-h BP monitoring[13]. From multiple linear regression of QKD according to SBP and heart rate, the theoretical value of the QKD for a SBP of 100 mm Hg and a heart rate of 60 beats/min is determined[14].

Li and colleagues assessed the correlation of AASI with carotid-femoral PWV in a group of 166 healthy Chinese volunteers[15]. A close relation was present between PWV and AASI ($r=0.51$, $P<0.0001$). Another study found a significant ($r=0.28$, $P<0.001$), albeit weaker ($P=0.004$, calculated by Fisher’s R-to-Z transform), correlation between PWV and AASI in 346 untreated hypertensive patients.[16] In 348 participants AASI correlated with the central and peripheral AIx and the 24 hour PP[15, 17]. AASI in comparison with the 24 hour PP, correlated more closely with the central ($r=0.48$ vs. 0.34, $P<0.001$) and the peripheral AIx ($r=0.50$ vs. 0.36, $P<0.001$). In subjects <40 years, the correlation between AASI and both central and peripheral AIx remained significant ($r=0.18$ and 0.19, $P<0.05$), unlike the correlation between PP and the central or peripheral AIx ($r=0.00$ and –0.02, both non-significant). In 469 hypertensive patients[14], AASI was significantly inversely correlated with the QKD ($r=–0.29$, $P<0.001$). The correlation coefficient between the AASI, PWV and AIx measures the strength of relation between variables, not the agreement between them. Therefore one study[18] examined the inter-correlations in 622 (391 untreated, 231 treated) hypertensive patients, adjusting for confounders like age and sex. Furthermore they used Bland-Altman analysis to determine the 95% confidence intervals for the AASI to predict PWV or the AIx. AASI was significantly correlated with PWV ($r=0.28$, $P<0.001$) and AIx ($r=0.24$, $P<0.001$), however when adjusted for age and gender, the significance was lost ($r=0.07$, $P=0.08$ for PWV and $r=0.04$, $P=0.22$ for AIx). These results were similar in treated and untreated subjects. The 95% confidence interval for the AASI to predict PWV and AIx was ±4.18 m/s and ±25.4% respectively. These studies proved that AASI had a substantial correlation with other commonly used markers of arterial stiffness. The AASI nevertheless is not interchangeable with the other measures, but rather mutually exclusive measures.

As PWV is the golden standard, we chose to compare this index, with the more easily determined AASI. Table 1 gives an overview of prognostic power of PWV and AASI in terms of cardiovascular risk stratification, in hypertensive patients or general populations. In the section ‘prospective studies’ later in this review we will focus in more detail on the prospective value of the AASI. Compared to the AASI, PWV seems to have best prognostic
value for cardiac mortality and events[5, 19-23]. For total cardiovascular mortality, cerebrovascular mortality and stroke, PWV and AASI have similar prognostic strength[5, 20, 22-25]. Alx does not independently predict cardiovascular disease in general populations or hypertensive patients[26]. In models including both measures of arterial stiffness, AASI was a better predictor of stroke than PWV, whereas PWV performed better in the prediction of a composite cardiovascular endpoint. These findings support that both indexes of arterial stiffness provide complementary information in cardiovascular risk stratification[27].

**Determinants of the AASI**

After multivariate correction, AASI showed to rise with female sex, higher age, higher mean arterial pressure and to diminish with higher 24-hour pulse rate and body height[15]. In the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcomes (n=7604)[28], it was confirmed in multivariate analyses, that AASI associated positively with age and 24-h mean arterial pressure and negatively with height and 24-h heart rate, in different sex and ethnicities. This study proved that a higher goodness of fit (r²) of the AASI regression line in individual subjects strengthens the association with its known determinants and enhances the statistical power of analyses involving AASI as marker of arterial stiffness. Therefore, the authors suggested that future reports of research on AASI might include a sensitivity analysis, excluding subjects with the r² value for the goodness of fit of the AASI regression line set at a threshold of 0.36, or higher. However, primary analyses should always include all subjects, because a very low r², e.g. uncoupling of SBP and DBP, might also reflect cardiovascular dysregulation.

Schillaci and colleagues stated that other factors than arterial stiffness may affect the regression slope of AASI and confound results[16]. AASI was significantly higher in non-dippers than dippers (0.44 vs. 0.29, P<0.001), and the correlation between relative nighttime BP reduction and AASI was significant both for DBP as SBP (0.46 and 0.28, both P-values <0.001). No significantly higher PWV was found in non-dippers, excluding arterial stiffness as the cause. Therefore they stated that nocturnal BP dipping is a possible confounder for AASI determination. It was confirmed in a Flemish population that AASI inversely correlated with the nocturnal BP fall, especially in ambulatory recordings with a disproportionately large number of nighttime readings[29]. It was proposed therefore to standardize the number of nighttime and daytime readings and to use regression weighted for the time interval between successive readings to remove the effect of the night-to-day ratio of the number of BP readings computing AASI. Strikingly, in contrary to Schillaci’s findings[16], nighttime dipping similarly influenced PWV and AASI measured within 24 hours (r=0.54 and 0.49 for systolic and r=0.56 and 0.57 for diastolic dipping, P-value of the difference = 0.54) in 166 Chinese volunteers[29].

Another group stated that the magnitude of nocturnal BP fall and thus AASI was associated with the correlation between SBP and DBP (r²)[30]. The Sym_AASI was created, calculated by 1 minus a so called symmetrical regression slope of SBP on DBP. This variant of AASI was less (but now significantly positive) associated with nocturnal dipping and not affected by the goodness of fit (r²) of the regression slope. Little evidence was presented for Sym_AASI in reflecting arterial stiffening or cardiovascular risk. These concerns proved justified in a Belgian cohort (n=1127)[31]. AASI was similarly associated with classical risk factors and stronger correlated than Sym_AASI with PP (r=0.50 vs. r=0.17, P<0.001)[32].
<table>
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<tr>
<th>Authors</th>
<th>Participants</th>
<th>N</th>
<th>Age (years)</th>
<th>Follow-up (years)</th>
<th>Outcome</th>
<th>Groups</th>
<th>events</th>
<th>Risk*</th>
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<tr>
<td><strong>AASI</strong></td>
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<tr>
<td>Dolan et al.[5]</td>
<td>Hypertensives</td>
<td>11291</td>
<td>54.6±14.6</td>
<td>5.3</td>
<td>CV mortality</td>
<td>G1: 1 SD increase</td>
<td>566 CV deaths; 151 fatal strokes</td>
<td>G1: CV deaths: 1.08 (0.98-1.19)</td>
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<td></td>
<td>G1: Stroke deaths</td>
<td>1.21 (1.01-1.45)</td>
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<tr>
<td>Kikuya et al.[22]</td>
<td>General population</td>
<td>1542</td>
<td>61.7±10.7</td>
<td>13.3</td>
<td>CV mortality</td>
<td>G1: &lt;0.39 U</td>
<td>126 CV deaths; 63 fatal strokes</td>
<td>G1: CV deaths: 1.41 (1.01-1.96)</td>
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<td>G2: 0.39-0.45</td>
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<td>G3: 0.45-0.51</td>
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<td>G4: &gt;0.51</td>
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<td>Hansen et al.[23]</td>
<td>General population</td>
<td>1829</td>
<td>55.5±10.7</td>
<td>9.4</td>
<td>CV events</td>
<td>G1: 1 SD increase (0.14 U)</td>
<td>212 CV events; 40 strokes</td>
<td>G1: CV events: 1.06 (0.91-1.23)</td>
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<td>G1: Stroke events</td>
<td>1.62 (1.14-2.28)</td>
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<tr>
<td>Gosse et al.[14]</td>
<td>Hypertensives</td>
<td>440</td>
<td>54 ± 13</td>
<td>5.8±3.2</td>
<td>CV events</td>
<td>G1: Tertile 1 vs. 2 G2: Tertile 1 vs. 3</td>
<td>Composite of unspecified CV events, CV death and non-CV death: 62</td>
<td>G1: Composite 1.5 (0.7-3.3)</td>
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<td>G2: Composite 2.8 (1.3-5.8)</td>
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<td><strong>PWV</strong></td>
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<td>Laurent et al.[57]</td>
<td>Hypertensives</td>
<td>1980</td>
<td>50±13</td>
<td>9.3±4.4</td>
<td>CV mortality</td>
<td>G1: +5 m/s increase</td>
<td>107 fatal events; 46 CV deaths</td>
<td>G1: CV mortality: 1.51 (1.08-2.11)</td>
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<td>G2: All cause: 1.34 (1.04-1.74)</td>
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<td>G1: CV mortality: 1.20 (1.01-1.41)</td>
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<td>G2 CHD: 1.16 (1.00-1.35)</td>
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<td>CV events: G2: 1.37 (0.83-2.29)</td>
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<td>G3: 1.93 (1.16-3.21)</td>
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<tr>
<td>Mattace-Raso et al.[58]</td>
<td>General population</td>
<td>945</td>
<td>71.7±6.7</td>
<td>4.1±0.8</td>
<td>CV events</td>
<td>Tertiles of PWV G1: Reference G2 G3</td>
<td>156 CV events; 63 strokes</td>
<td>G2: Stroke events: 1.20 (0.56-2.75)</td>
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<td>G3: 1.96 (0.94-4.29)</td>
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</table>

CV, cardiovascular; CHD, coronary heart disease; AASI, Ambulatory Arterial Stiffness Index; PWV, Pulse Wave Velocity. *All studies used Hazard Ratios (HR) to calculate risk except for Laurent et al. who used Odds Ratios (OR).
Reproducibility and heritability of AASI

In the Ohasama study population[22], a mean number of 46 readings were available per recording for the calculation of AASI. AASI seemed less reproducible when the number of readings in ambulatory blood pressure decreased, but this did not affect the predictive accuracy of AASI for cardiovascular mortality, until the median number of readings per ABP recording was less than ~35. This number should be regarded as the minimum of readings performed in 24-h ABPM to determine AASI. Further, it should be prevented to have a disproportional number of daytime or nighttime readings, as this could influence the AASI[33].

In a study consisting of 145 isolated systolic hypertensives from the Syst-Eur trial[34] and 152 patients with systolic and/or diastolic hypertension, referred to an outpatient clinic (Radboud University Medical Centre Nijmegen), the repeatability of AASI and 24-h PP within a period of 3 months was investigated. Mean age was 46.2 and 71.0 years and the median interval between measurements was 8 and 31 days for the Nijmegen and Syst-Eur populations, respectively. In the Nijmegen patients, the repeatability coefficients (RC) of AASI and 24-h PP, expressed as twice the SD of the within-subject differences between repeat recordings as a percentage of 4 times the SD of the mean of the paired measurements, were ~50%. In Syst-Eur patients, the corresponding values of the RC were ~60% for AASI and ~40% for PP. Sensitivity analyses stratified for type of hypertension, or dipping status did not significantly change RC’s for AASI, as they were in the 50%–60% range. The authors concluded AASI was modestly reproducible.

A French group investigated the reproducibility of AASI and QKD in 38 volunteers within 2 weeks[14]. QKD showed better reproducibility ($r = 0.79$, SD of differences [SDD] = 9 msec, coefficient of variation [CV] = 4%) than AASI ($r = 0.21$, SDD = 0.15, CV = 25%). Unfortunately, no statistical test and associated $P$-value was presented for the comparison of the reproducibility. Moreover, the CV does not account for the possible range of biological variation. Had the SDD been expressed as a percentage of near maximal variation in a measurement, as given by four times the SD[35], the conclusion of reproducibility might have been quite different[36].

One study investigated the heritability of AASI in 260 siblings from 118 families in Sweden[37]. Before adjustment for significant covariates the heritability of AASI was 41% ($P=0.009$), which decreased to 28% ($P=0.05$) after adjustment for age, 24-h PP and 24-h pulse rate. After adjustment of 24-h PP for AASI, age sex and BMI, the heritability decreased from 63 to 55% ($P=0.002$). This study showed that AASI is partially heritable and confirms that arterial stiffness is under genetic control[38, 39]. The authors stated that AASI and 24-h PP might reflect partially different aspects of arterial stiffness and that the power of genetic studies aiming at finding genes of importance for arterial stiffness would be significantly increased by including both of the two surrogate markers as phenotypes.

Cross-sectional studies

An Italian study investigated if AASI relates to the asymptomatic and potentially reversible early phase of cardiovascular disease[40]. Leoncini and colleagues recruited 188 previously untreated primary hypertensives and explored the association of AASI with microalbuminuria, left ventricular hypertrophy and carotid atherosclerosis[41]. They measured albuminuria as the albumin to creatinine ratio (ACR), left ventricular mass index (LVMI) by echocardiography and carotid abnormalities by ultrasonography. AASI was significantly related to early signs of target organ damage (TOD), such as urinary albumin excretion ($\rho=0.234; \ P=0.002$) and carotid intima-media-thickness ($r=0.196; \ P=0.016$),
whereas the correlation between AASI and LVMI, did not reach statistical significance \((r=0.133; P=0.086)\). Schillaci and colleagues also investigated the relation between AASI and LVMI and demonstrated a significant correlation between AASI and LVMI \((r=0.17, P<0.001)\)[16].

As the global burden of cardiovascular risk runs in parallel with abnormalities in renal function[42, 43], Ratto and colleagues[40] focussed on (early) signs of renal damage, namely albuminuria, as measured by ACR, creatinine clearance, estimated using the Cockgroft-Gault formula (eGFR), and the interlobar resistive index, evaluated by renal ultrasound and Doppler examination. They related these measures to AASI in 168 untreated patients with sustained primary hypertension. AASI correlated positively to urinary albumin excretion \((r=0.212; P=0.0074)\) and resistive index \((r=0.176; P=0.0377)\), and was negatively associated with eGFR \((\rho=0.253; P=0.0018)\) and with the renal volume to the resistive index ratio \((r=0.203; P=0.0184)\), a marker of nephroangiosclerosis. Even after adjustment for confounding factors, patients with target organ involvement had a higher AASI than those who did not, and each SD increase in AASI roughly doubled the risk of having subclinical organ damage.

Palmas and colleagues compared the value of PP and AASI in predicting deterioration of renal function, as measured by ACR[44], in a multiethnic cohort of 1180 type-2 diabetic subjects. The main finding of this study was that, in the fourth quartile of the population, AASI was associated with a higher ACR at follow-up after adjustment for several covariates, including office PP \((P=0.024)\). However, this association weakened to a non-significant level after replacing office PP with 24-hour PP \((P=0.38)\), whereas 24-hour PP retained its status as independent predictor after full adjustment \((P=0.001)\). In this high risk (overweight, mean BMI 31.5 and advanced age, mean ≈ 70 years) population, AASI was only modestly associated with progression of albuminuria, as compared to 24-hour PP.

Others evaluated the relationship between AASI and glomerular filtration rate (GFR), in 143 untreated hypertensive patients without CV complications and without severe renal insufficiency[45]. Mean (± SD) GFR (assessed by a radioisotopic technique) was 110.5 ± 33.4 ml/min/1.73 m². A significant inverse correlation between AASI and GFR was found \((r = -0.30; P<0.001)\). This association was also observed in a multiple regression model with parameters age, gender, HDL cholesterol, body mass index, 24-h PP, and day-night diastolic (or systolic) reduction in BP. In this model, only AASI maintained a statistically significant \((P = 0.02)\) association with GFR. The authors hypothesized that this finding may in part help to explain the increased risk for CV morbidity and mortality documented in subjects with mild-to-moderate renal dysfunction.

The relationship between AASI and the metabolic syndrome (MS) was investigated in 156 untreated non diabetic hypertensives[46]. The prevalence of MS was 23% \((n=36)\). After adjustment, AASI was significantly higher in MS \((0.53 \text{ vs. } 0.48, P=0.03)\). Each SD (0.16 units) increase in AASI entailed an almost twofold risk of having MS \((\text{OR } 1.73, 95\% \text{ CI } 1.07-2.79)\). The prevalence of MS resulted in a more than twofold risk \((\text{OR } 2.63, 95\% \text{ CI } 1.22-5.71)\) for an increased AASI \((>0.55 \text{ units})\).

Comprehensively, these findings underscore that AASI holds the ability to predict TOD, although it was not always superior to 24-h PP. This suggests that this new marker might be an appropriate instrument for detecting patients at an early stage of the disease process in order to prevent cardiovascular events.
**Prospective studies**

The first prospective study regarding AASI included 11291 untreated subjects from Ireland and monitored cardiovascular mortality, from 1980 to 2002.[5] Mean follow-up time was 5.3 years and 566 cardiovascular deaths occurred. Baseline AASI and pulse pressure (PP) significantly predicted cardiovascular mortality, after multivariate correction for other risk factors (hazard ratio (HR) of 1 SD increase with 95% CI, 1.14 (1.04-1.24), \( P < 0.01 \)). In adjusted analyses dichotomized as normal/abnormal values (under/above 95\(^{th}\) percentile) of AASI and PP, AASI independently predicted cardiovascular (HR with 95% CI, 1.71 (1.33-2.19), \( P < 0.001 \)), cardiac (1.44 (1.03-2.00), \( P < 0.05 \)) and stroke mortality (2.49 (1.64-3.80), \( P < 0.001 \)). PP only predicted cardiac mortality (1.34 (1.05-1.71), \( P < 0.05 \)). When PP and AASI were additionally corrected for each other, only AASI remained significantly predictive for total cardiovascular and stroke mortality, whereas PP lost significance. Moreover, AASI significantly predicted cardiovascular and stroke mortality in both hypertensives and normotensives, whereas PP only predicted cardiac mortality in hypertensives. This study demonstrated the ability of AASI to predict various forms of cardiovascular mortality for the first time. AASI could be extra useful in low risk populations, as it was especially predictive in normotensives.

In a second prospective study AASI was evaluated in terms of fatal and non-fatal cardiovascular complications in a cohort with 1829 randomly selected participants from the Copenhagen County (Denmark)[23]. Median follow-up was 9.4 years and included 60 cardiovascular deaths, 128 coronary events, and 24 strokes. While after full adjustment, AASI remained independently and significantly predictive for fatal and non-fatal stroke (HR of 1 SD increase with 95% CI, 1.62 (1.14-2.28), \( P < 0.01 \)), PP lost its value for all three outcome measures. This study validated AASI in terms of cardiovascular mortality and extended the prognostic value of AASI in terms of cardiovascular events. In 1678 Danes (mean age 54.8 years) from the same cohort PWV, which is regarded as the golden standard for the non-invasive measurement of arterial stiffness, was measured within 24 hours and directly compared to AASI. In multivariate-adjusted Cox regression models including both indexes, AASI (standardized hazard ratio, 1.68; \( P = 0.01 \)) but not PWV (0.91; \( P = 0.62 \)) predicted stroke, whereas the opposite was true for the composite of all cardiovascular events (PWV, 1.15; \( P = 0.03 \) and AASI, 1.04; \( P = 0.68 \)). This study was the first that included both AASI and PWV in the same Cox model and provided evidence for the independent contributions of both measures of arterial stiffness to cardiovascular risk stratification.

Although AASI might ameliorate risk stratification based on ambulatory blood pressure measurements, its use cannot be recommended before the outcome results are replicated in population cohorts of different ethnic extraction. Therefore a comparable study was initiated in a population cohort of Asian ethnicity[22]. AASI and PP were related to mortality in 1542 randomly recruited Ohasama residents (Japan). Almost half of the patients had ambulatory hypertension, of whom 62% used antihypertensives. Median follow-up was 13.3 years and 126 cardiovascular (63 stroke, 59 cardiac) deaths occurred. The sex- and age-standardized incidence rates of cardiovascular and stroke mortality across quartiles were U-shaped for AASI and J-shaped for PP. Across quartiles, the multivariate-adjusted HR for cardiovascular and stroke mortality were significant and U-shaped for AASI, whereas for PP significance was lost. The hazard ratios for cardiovascular mortality (versus overall risk in the whole population) across ascending AASI quartiles were 1.41 (\( P = 0.04 \)), 0.85 (\( P = 0.25 \)), 0.65 (\( P = 0.01 \)), and 1.29 (\( P = 0.03 \)). That study[22] confirmed the results of previous studies[5, 23] analysing the predictive capabilities of AASI on cardiovascular outcome and extended the validation to a general population of Asian extraction. Striking were the U-shaped incidence rates of cardiovascular and stroke mortality across quartiles, which were confirmatory even
after exclusion of several subgroups. One could speculate that other risk factors, like physical activity, nutrition and psychosocial factors, for which no adjustments could be made, may have contributed to this distribution[47, 48]. Further, use of antihypertensives or genetic differences could account for the differences in this population.

A French group investigated AASI in terms of a composite endpoint (unspecified cardiovascular death, non-cardiovascular death, and cardiovascular events) in 440 hypertensive patients without a history of cardiovascular disease, referred to a clinic for antihypertensive treatment. Mean follow-up was 70 ± 39 months and a composite of 62 events were recorded. AASI was directly compared to the QKD interval[13], which is derived from the time between the QRS-wave on the electrocardiogram and the detection of the last Korotkoff sound during deflation of the cuff in 24-h BP monitoring. This value is inversely related to arterial stiffness. In age adjusted analysis, participants in the highest tertile vs. the lowest tertile of AASI had a RR of 2.8 (95% CI 1.3-5.8, P=0.01). For the QKD the RR was 6.9 (95% CI 2-23) in the lowest vs. the highest tertile. When age and 24-h PP were included in the model, only QKD remained significantly (RR 4.7, 95% CI 1.4-16, P=0.04) linked to the composite endpoint. Regrettably, no continuous analysis was present for the risk estimations, no sensitivity analyses were made for cardiovascular disease and no statistical test was provided to compare the QKD to the AASI.

**Viewpoints and future of AASI**

O’Brien stressed in an editorial that AASI extends the usefulness of ABPM[49]. Besides providing prognostic information through circadian blood pressure variation, assessment of white coat and masked hypertension, additionally arterial stiffness could be determined in assessing cardiovascular risk.

A lively debate was initiated whether the AASI purely reflected arterial stiffness or additionally other entities[16, 32, 33, 50-53]. Physiological assumptions were used to rewrite AASI in a complex formula (AASI=1-(3-T/τ) / (3+2T/τ) = (T/τ) / (1+2T/3τ))[53], with T as R-R interval of the heart and τ as aortic decay time in diastole. The conclusion of this mathematical approach, was that AASI was not only a measure of arterial stiffness, but also dependent on systemic peripheral resistance, heart period and blood pressure. Therefore the authors stated that AASI was a ventriculo-arterial coupling factor, rather than an exclusive measure of arterial stiffness. Benetos and Lacolley considered the fact that peripheral resistance varies over the day[54], hereby influencing AASI and diminishing its ability to determine arterial stiffness. Mean arterial pressure, a rough marker of small artery resistance, predicts stroke better than PP, which predicts cardiac events better. In this line of thinking the authors hypothesised that the possible influence of small artery resistance on AASI is the reason why it is more predictive for stroke than cardiac events.

Possible future work on AASI might include the assessment of other confounders in the determination of AASI. An overview of the literature depicts important differences in mean AASI, which can not be entirely attributed to determinants like age, sex, cardiovascular history, hypertensive and diabetic status and arterial pressure[55]. Other factors, like study set-up and methods for determining AASI, could possibly account for these differences. Therefore, AASI determination should be standardized. After doing so, cut-off values for AASI should be created in different sex, ethnicity and age. AASI should be tested prospectively, with sensitivity analyses using cut-off values for the goodness of fit of the regression line (r²), or other modifications. These developments could further refine AASI’s prognostic quality. Further, it should be investigated if AASI has additional value in clinical decision making, in different populations and patients and different disease conditions.
Finally, it should be investigated, if the AASI is influenced by treatment, and if this is in accordance with improved (cardiovascular) outcome. Only in this way, AASI could develop into a stable, firmly rooted marker of cardiovascular risk.

**Perspectives**
Recently, AASI was introduced as a new indirect marker of arterial stiffness[5], which can easily be computed from 24 hour ABPM and does not necessitate any extra equipment or observer training. In prospective and cross-sectional studies, AASI proved to predict total cardiovascular mortality, fatal and non-fatal stroke and target organ damage, over and beyond classical risk factors[5, 22, 23, 27, 40, 41, 56]. AASI proved to be significantly related to other measures of arterial stiffness, and complementary to the other measures in providing cardiovascular risk[5, 27]. Further standardization and refinement could extend the AASI into an important marker in cardiovascular risk estimation.

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**Disclosures**
None.
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Part 3

Procession of blood pressure: The Ambulatory Arterial Stiffness Index

Chapter 4.2

Reproducibility of the ambulatory arterial stiffness index in hypertensive patients.

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Jiguang Wang
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Theo Thien
Jan A. Staessen

Abstract

**Background** We studied the repeatability of the ambulatory arterial stiffness index (AASI), which can be computed from 24-h blood pressure (BP) recordings as unity minus the regression slope of diastolic on systolic BP.

**Methods** One hundred and fifty-two hypertensive outpatients recruited in Nijmegen (mean age 46.2 years; 76.3% with systolic and diastolic hypertension) and 145 patients enrolled in the Systolic Hypertension in Europe (Syst-Eur) trial (71.0 years) underwent 24-h BP monitoring at a median interval of 8 and 31 days, respectively. We used the repeatability coefficient, which is twice the SD of the within-participant differences between repeat recordings, and expressed it as a percentage of four times the SD of the mean of the paired measurements.

**Results** Mean AASI (crude or derived by time-weighted or robust regression) and 24-h pulse pressure (PP) were similar on repeat recordings in both cohorts. In Nijmegen patients, repeatability coefficients of AASI and PP were ≈50%. In Syst-Eur trial patients, repeatability coefficient was ≈60% for AASI and ≈40% for PP. For comparison, repeatability coefficients for 24-h systolic and diastolic BP were ≈30%. Differences in AASI between paired recordings were correlated with differences in the goodness of fit (r²) of the AASI regression line as well as with differences in the night-to-day BP ratio. However, in sensitivity analyses stratified for type of hypertension, r², or dipping status, repeatability coefficients for AASI did not widely depart from 50 to 60% range.

**Conclusion** Estimates of mean AASI were not different between repeat recordings, and repeatability coefficients were within the 50–60% range.
Introduction

Increased arterial stiffness of the large arteries predicts cardiovascular complications over and beyond blood pressure (BP) and classical cardiovascular risk factors [1]. Nevertheless, risk stratification based on arterial stiffness remains underused in clinical practice because most techniques to measure arterial properties require expensive equipment and highly trained observers. We recently proposed the ambulatory arterial stiffness index (AASI) as a measure reflecting arterial stiffness [2,3]. This novel index, defined as one minus the regression slope of diastolic on systolic BP in individual subjects, can be determined from 24-h ambulatory BP recordings [2,3]. To date, several cross-sectional studies [4,5] and at least three prospective cohort studies [3,6,7] demonstrated an association of AASI either with signs of target organ damage in never-treated hypertensive patients [4] or with the incidence of cardiovascular mortality and morbidity[3,6,7]. When adjusted for pulse pressure (PP) [3,6,7] or aortic pulse wave velocity [8], AASI remained predictive, in particular of stroke.

To our knowledge, no previous publication has addressed the reproducibility of AASI as determined from repeat ambulatory BP recordings. We investigated the reproducibility of AASI in patients with systolic and/or diastolic hypertension recruited in Nijmegen and in older patients with isolated systolic hypertension enrolled in a substudy to the Systolic Hypertension in Europe (Syst-Eur) trial.

Methods

Study population

Patients referred to the outpatient clinic of the University Medical Centre St Radboud, Nijmegen, the Netherlands[9], and patients enrolled in the substudy on ambulatory BP measurement to the Syst-Eur trial [10] qualified for the present analysis, if they had undergone repeat 24-h ambulatory recordings within 2 months, while being untreated [9,10] or minimally treated [9] with no change in treatment status between the first and repeat recording.

Nijmegen cohort

At the Nijmegen outpatient clinic, doctors discontinued BP-lowering drugs in newly referred patients, except when there was a compelling indication, such as the use of b-blockers in patients with angina pectoris (‘minimal treatment’). The office BP was then reassessed by obtaining three consecutive measurements at two to three follow-up visits. Of 1325 consecutive patients attending the Nijmegen clinic, 275 underwent repeat ambulatory BP measurement within 2 months. Of those, we excluded 33 (12.0%) from analysis because their treatment status changed between the first and repeat recording, and 56 (20.4%) because over the whole day the mean interval between the ambulatory BP readings was shorter than 15 min or longer than 45 min.

The Systolic Hypertension in Europe trial cohort

Previous publications describe the protocol of the Syst-Eur trial in detail [10]. Eligible patients were aged 60 years or older. They had a sitting BP ranging from 160 to 219mmHg systolic and less than 95mmHg diastolic. The standing systolic BP had to be at least 140mmHg. Of 837 patients [10] enrolled in the substudy on ambulatory BP monitoring, 153 (18.3%) had repeat recordings within 2 months, while taking placebo.
Blood pressure measurement
Trained observers measured the patients’ office BP at repeated visits. To describe the patients’ conventional BP, we used the average of six to nine readings (three readings at two to three visits) in the Nijmegen cohort [9] and the average of six readings (two readings at three visits) in Syst-Eur trial patients [10]. For the definition of hypertension in the sensitivity analyses, we applied current guidelines [11]. Isolated systolic hypertension was a BP of 140mmHg systolic or higher with diastolic BP below 90mmHg.

For analysis, we considered ambulatory BP recordings with the interval between successive readings programmed at intervals from 15 to 30 min during daytime and from 30 to 60 min during nighttime. We only analysed recordings with at least five readings between midnight and 06:00 h. In addition, we required that the recordings included at least 15 daytime readings. On the basis of these quality criteria, we excluded 34 patients from the Nijmegen cohort (12.4%) and eight Syst-Eur trial patients (5.2%). Thus, the number of patients analysed totalled 297, that is 152 patients from Nijmegen and 145 Syst-Eur trial patients.

The validated monitors used in Nijmegen were the auscultatory Oxford Medilog (Oxford Medical Systems Ltd, Oxford, UK [12]) in 54 patients (35.5%), the oscillometric Mobil O Graph (I.E.M., Stolberg, Germany [13]) in 43 patients (28.3%), and the oscillometric SpaceLabs 90207 (SpaceLabs Inc., Redmond, Washington, USA [14]) in 55 patients (36.2%). The monitors fitted to Syst-Eur trial patients were the oscillometric SpaceLabs 90202 [14] or 90207 [15] in 49 patients (35.5%) and 78 patients (56.5%), respectively, and the auscultatory TakedaTM2420 (A&D, Tokyo, Japan [16]) in 11 patients (3.7%).

The same SAS macro processed all ambulatory recordings, which stayed unedited. For the sensitivity analysis involving dipping status, we defined daytime and nighttime in both cohorts as the intervals ranging from 10:00 to 20:00 h and from midnight to 06:00 h, respectively [17,18]. We weighted the individual means of the ambulatory BP by the interval between readings.

From individual 24-h recordings, we computed the regression slope of diastolic on systolic BP. We defined the AASI as one minus the regression slope (crude AASI). We used the coefficient of determination ($r^2$) as a measure of the goodness of fit of the AASI regression line. We also computed AASI, using time-weighted or robust regression (least trimmed squares).

Statistical methods
For database management and statistical analysis, we used SAS software (version 9.1.3; SAS Institute, Cary, North Carolina, USA). For comparison of means, we applied the Student’s t-test for paired or unpaired observations, as appropriate. For comparison of proportions between groups, we applied the $x^2$-statistic. Statistical significance was an a-level of 0.05 on two-sided tests.

We assessed the agreement between paired ambulatory recordings by Bland and Altman’s approach [19,20]. For the evaluation of reproducibility, we used the repeatability coefficient, which is twice the SD of the within-participant differences between repeat recordings (repeat minus first) [21]. This measure is specifically designed to evaluate within-participant reproducibility. To take into consideration the normal biological variation of a measure, we expressed the repeatability coefficient as a percentage of close to maximal variation (four times the SD of the mean of the duplicate measurements). By this, a reasonable comparison of the repeatability of different measures can be undertaken.
We also applied single and multiple regression analysis. In stepwise regression, we set the P-value for independent variables to enter and to stay into models at 0.15. We studied the coincidence of regression lines by analysis of covariance, as described by Kleinbaum et al.[22].

**Results**

**Patient characteristics**

Table 1 lists the main clinical characteristics of the two study cohorts. Both groups of patients included nearly 60% of women. Compared with Syst-Eur trial patients, the Nijmegen patients were younger (46.2 versus 71.0 years), taller (170 versus 162 cm), heavier (77.9 versus 69.4 kg), but had similar body mass index (26.8 versus 26.4 kg/m²).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nijmegen</th>
<th>Syst-Eur</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>152</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) of characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.2 ± 13.6</td>
<td>71.0 ± 6.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.9 ± 15.3</td>
<td>69.4 ± 13.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 9</td>
<td>162 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.8 ± 4.7</td>
<td>26.4 ± 4.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Office systolic BP (mmHg)</td>
<td>168.6 ± 25.1</td>
<td>178.4 ± 16.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Office diastolic BP (mmHg)</td>
<td>101.2 ± 11.4</td>
<td>85.4 ± 9.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse rate (beats per minute)</td>
<td>72.9 ± 12.5</td>
<td>73.5 ± 11.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Number of participants (%) with characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>89 (58.6)</td>
<td>89 (61.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>21 (14.2)</td>
<td>15 (10.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Drinking alcohol, n (%)</td>
<td>22 (14.5)</td>
<td>34 (23.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>On BP lowering drugs, n (%)</td>
<td>18 (11.8)</td>
<td>0 (0.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (7.2)</td>
<td>11 (7.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Classification of hypertension*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated systolic, n (%)</td>
<td>17 (11.2)</td>
<td>100 (69.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isolated diastolic, n (%)</td>
<td>12 (7.9)</td>
<td>0 (0.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mixed, n (%)</td>
<td>116 (76.3)</td>
<td>44 (30.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>22 (14.5)</td>
<td>44 (30.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P values are for the differences between the patients enrolled in the Nijmegen cohort and in the Syst-Eur trial. AASI, ambulatory arterial stiffness index. *A total of seven patients in Nijmegen and one from the Systolic Hypertension in Europe (Syst-Eur) trial were not hypertensive on clinic blood pressure (BP) measurement when taking into account current hypertension guidelines.

In line with the recruitment criteria based on office BP, Syst-Eur compared with Nijmegen patients (Table 1) had higher systolic BP (178.4 versus 168.6mmHg) on conventional measurement, but lower diastolic BP (85.4 versus 101.2mmHg). A history of cardiovascular disease was more prevalent among the older Syst-Eur trial patients (30.3 versus 14.5%). Table 2 shows that Syst-Eur trial patients on average had higher AASI than Nijmegen patients, irrespective of the way AASI was computed (all P<0.008).
Repeatability of ambulatory measurements

Figure 1 provides Bland and Altman plots for the crude AASI in Nijmegen and Syst-Eur trial patients, respectively. Detailed repeatability statistics appear in Table 2.

Reproducibility of the ambulatory arterial stiffness index (crude AASI) in patients enrolled in the Nijmegen and Syst-Eur trial cohorts. The difference of the second minus the first measurement of AASI was plotted against the mean of the repeat measurements (Bland–Altman plot). The full and dotted lines represent the mean difference and the limits of agreement (mean ± 2 SD, respectively). Outliers were plotted at ±0.35. AASI, arterial stiffness index.

Table 2 Differences between repeat minus first ambulatory measurement

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Repeat</th>
<th>P</th>
<th>ΔAbsolute</th>
<th>95% CI</th>
<th>RC</th>
<th>pMV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nijmegen (n = 152)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Crude AASI</td>
<td>0.47±0.16</td>
<td>0.45±0.17</td>
<td>0.13</td>
<td>−0.02±0.16</td>
<td>−0.04 to -0.01</td>
<td>0.32</td>
<td>55</td>
</tr>
<tr>
<td>Time weighted AASI</td>
<td>0.47±0.16</td>
<td>0.43±0.17</td>
<td>0.10</td>
<td>−0.02±0.16</td>
<td>−0.06 to -0.01</td>
<td>0.32</td>
<td>55</td>
</tr>
<tr>
<td>Robust AASI</td>
<td>0.43±0.17</td>
<td>0.42±0.19</td>
<td>0.28</td>
<td>−0.01±0.15</td>
<td>−0.04 to -0.01</td>
<td>0.30</td>
<td>48</td>
</tr>
<tr>
<td>24-h systolic BP (mmHg)</td>
<td>150.1±19.2</td>
<td>146.6±18.4</td>
<td>0.06</td>
<td>−1.51±10.7</td>
<td>−3.22 to 0.21</td>
<td>21.4</td>
<td>30</td>
</tr>
<tr>
<td>24-h diastolic BP (mmHg)</td>
<td>94.2±13.1</td>
<td>92.7±12.6</td>
<td>0.009</td>
<td>−1.43±6.69</td>
<td>−2.50 to -0.36</td>
<td>13.4</td>
<td>27</td>
</tr>
<tr>
<td>24-h PP (mmHg)</td>
<td>56.0±12.1</td>
<td>55.9±12.5</td>
<td>0.88</td>
<td>−0.08±7.00</td>
<td>−1.15 to 0.99</td>
<td>14.0</td>
<td>52</td>
</tr>
<tr>
<td><strong>Syst-Eur trial (n = 149)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude AASI</td>
<td>0.52±0.19</td>
<td>0.51±0.20</td>
<td>0.40</td>
<td>−0.02±0.20</td>
<td>−0.06 to -0.02</td>
<td>0.40</td>
<td>61</td>
</tr>
<tr>
<td>Time weighted AASI</td>
<td>0.52±0.20</td>
<td>0.51±0.20</td>
<td>0.29</td>
<td>−0.02±0.20</td>
<td>−0.05 to -0.02</td>
<td>0.40</td>
<td>61</td>
</tr>
<tr>
<td>Robust AASI</td>
<td>0.50±0.16</td>
<td>0.54±0.15</td>
<td>0.66</td>
<td>−0.01±0.14</td>
<td>−0.03 to -0.02</td>
<td>0.32</td>
<td>62</td>
</tr>
<tr>
<td>24-h systolic BP (mmHg)</td>
<td>154.7±16.4</td>
<td>153.4±15.7</td>
<td>0.09</td>
<td>−1.30±9.11</td>
<td>−2.76 to 0.20</td>
<td>18.2</td>
<td>31</td>
</tr>
<tr>
<td>24-h diastolic BP (mmHg)</td>
<td>81.1±9.7</td>
<td>80.4±8.9</td>
<td>0.12</td>
<td>−0.71±5.95</td>
<td>−1.66 to 0.19</td>
<td>11.9</td>
<td>33</td>
</tr>
<tr>
<td>24-h PP (mmHg)</td>
<td>73.6±12.2</td>
<td>73.0±12.9</td>
<td>0.24</td>
<td>−1.45±9.21</td>
<td>−1.71 to 0.22</td>
<td>18.4</td>
<td>37</td>
</tr>
</tbody>
</table>

Plus–minus values are mean ± SD. Absolute differences (Δ) were computed as repeat minus first recording. The repeatability coefficient (RC) is twice the SD of the signed differences between the duplicate measurements. RC was also expressed as a percentage of four times the SD of the mean of the paired recordings (pMV). AASI, ambulatory arterial stiffness index; BP, blood pressure; CI, confidence interval; PP, pulse pressure; Syst-Eur, Systolic Hypertension in Europe.

Nijmegen cohort

The median interval between the first and repeat ambulatory recording was 8 days [range=4–60 days; interquartile range (IQR)=7–15 days]. AASI, time-weighted AASI, robust AASI and 24-h PP were similar on first and repeat measurement (P≥0.10; Table 2). The 24-h diastolic BP was significantly lower on repeat than first recording (−1.43mmHg; P=0.009) with a similar trend for the 24-h systolic BP (−1.51mmHg; P=0.09). The repeatability of AASI and 24-h PP expressed as a percentage of the near maximal variation in these measurements (the interval corresponding with 2SD around the mean of the repeat recordings) ranged from approximately 45 to 55%. The corresponding repeatability estimate for the 24-h systolic and diastolic BP was around 30% (Table 2).
In Nijmegen patients, the differences between repeat minus first crude AASI correlated inversely with the differences in the goodness of fit of the AASI regression line ($r = -0.77; P<0.0001$) and the changes in the night-to-day ratios of diastolic BP ($r = -0.29; P=0.0003$), but not systolic BP ($r = -0.12; P=0.14$). In multiple regression analyses, with mutual adjustments for these covariates, the corresponding partial correlation coefficients were $-0.76 (P<0.0001)$, $-0.25 (P=0.003)$, and $-0.25 (P=0.002)$, respectively.

The Systolic Hypertension in Europe trial patients

The median interval between the first and repeat ambulatory recording was 31 days (range=2–57 days; IQR=28–35 days). AASI, time-weighted AASI, robust AASI, 24-h PP and 24-h systolic and diastolic BP were similar on first and repeat measurement ($P \geq 0.09$; Table 2). Estimates of repeatability expressed as a percentage of near maximal variation were close to 60% for AASI, around 40% for the 24-h PP, and approximately 30% for 24-h systolic and diastolic BP (Table 2).

In Syst-Eur trial patients, the differences between repeat minus first crude AASI correlated inversely with the differences in the goodness of fit of the AASI regression line ($r = -0.57; P=0.0001$) and those in the night-to-day ratios of diastolic BP ($r = -0.25; P=0.003$) with a similar trend for the differences in the night-to-day ratio of systolic BP ($r = -0.15; P=0.07$). The corresponding partial correlation coefficients with mutual adjustment for these covariates were $-0.55 (P<0.0001)$, $-0.30 (P=0.001)$, and $-0.23 (P=0.006)$, respectively.

Comparison of repeatability between Nijmegen and the Systolic Hypertension in Europe trial patients

None of the differences in the estimates of repeatability among paired recordings between Nijmegen and Syst-Eur trial patients reached significance for any of the variables listed in Table 2 ($P \geq 0.10$). For the sensitivity analyses, we therefore pooled Nijmegen and Syst-Eur trial patients. The regression lines for the differences among the paired recordings in crude AASI versus those in the goodness of fit of the AASI regression lines were not coincident in Nijmegen and Syst-Eur trial patients because the slope was steeper in the Nijmegen patients ($P=0.008$; Fig. 2). In contrast, the regression lines for the differences among the paired recordings in crude AASI versus those in the night-to-day BP ratio were coincident ($P \geq 0.70$; Fig. 3).

Sensitivity analyses

Table 3 shows sensitivity analyses, according to the type of hypertension, dipping status, and the $r^2$ of the AASI regression line. In these analyses, we defined nondipping as a diastolic night-to-day BP ratio higher than 0.90. For the goodness of fit of the AASI regression line, we used 0.36 as the cut-off threshold, because the association of AASI with four determinants of arterial stiffness increased curvilinearly with $r^2$, with most of the improvement in the association occurring above a value of $r^2$ of 0.36.

Discussion

The key finding of our study was that AASI as determined from ambulatory BP recordings repeated within an interval of 2 months had moderate reproducibility. Mean values of AASI were similar in paired recordings. The repeatability coefficient, which is a measure for reproducibility within individual participants, was within the 50–60% range, which is better than for other parameters derived from the diurnal BP profile[23].
For comparison, the repeatability coefficients of the 24-h systolic and diastolic BPs in the current study were close to 30%, but diastolic BP in the Nijmegen cohort showed significant regression to the mean with lower values of the 24-h diastolic BP on repeat recording. PP, the QRS-Korotkoff-delay (QKD) index standardized to a systolic BP of 100 mmHg and a heart rate of 60 beats per minute (QKD100–60), the systolic augmentation index and pulse wave...
velocity are other non-invasive measures of arterial stiffness. Stergiou et al. [24] investigated the reproducibility of 24-h PP from repeat ambulatory BP recordings in 133 untreated hypertensive patients. The SD of the paired differences was 4mmHg compared with 7 and 9mmHg in our Nijmegen and Syst-Eur trial patients, respectively. In Stergiou’s study, the 24-h PP averaged (±SD) 47.5±7.4 and 46.4±7.9mmHg on first and repeat measurement. The nonreported P-value for the difference (−1.1mmHg) was therefore 0.0015 [1/(4/133^0.5)]. We estimated that in Stergiou’s study the repeatability coefficient expressed as a percentage of near maximal variation was approximately 27% [24], which at first sight seems somewhat smaller than in our Syst-Eur trial patients (37%). However, in 16 of Stergiou’s patient who were older than 60 years, the SD of the paired differences in the 24-h PP was 5mmHg [24], which would have yielded a repeatability estimate almost identical to that in our Syst-Eur trial cohort.

| Table 3 Differences between repeat minus first ambulatory measurement in subgroups |
|---------------------------------|----------|----------|----------|----------|----------|----------|
| Type of hypertension            | First    | Repeat   | P        | ΔAbsolute| 95% CI   | RC       |
| Isolated systolic (n=117)       | 0.54±0.19| 0.51±0.19| 0.09     | −0.03±0.19 | −0.06 to 0.01 | 0.38 64  |
| Isolated diastolic (n=123)      | 0.26±0.16| 0.43±0.17| 0.09     | 0.07±0.13  | −0.01 to 0.15 | 0.26 43  |
| Mixed systolic and diastolic (n=160) | 0.46±0.16| 0.46±0.18| 0.25     | −0.02±0.17 | −0.04 to 0.01 | 0.34 51  |
| Dipping status                  |          |          |          |          |          |          |
| Consistent dipper (n=198)       | 0.46±0.17| 0.45±0.13| 0.18     | −0.02±0.17 | −0.04 to 0.01 | 0.34 57  |
| Consistent nondipper (n=31)     | 0.61±0.15| 0.60±0.22| 0.25     | −0.01±0.21 | −0.08 to 0.07 | 0.42 67  |
| Inconsistent between recordings  |          |          |          |          |          |          |
| (n=68)                          |          |          |          |          |          |          |
| Dipper to nondipper (n=87)      | 0.50±0.18| 0.54±0.17| 0.28     | 0.04±0.18  | −0.03 to 0.11 | 0.36 55  |
| Non-dipper to dipper (n=31)     | 0.64±0.17| 0.49±0.16| 0.25     | −0.05±0.17 | −0.12 to 0.01 | 0.34 49  |
| Goodness of fit of AASI regression line |          |          |          |          |          |          |
| P<0.36 in two recordings (n=75) | 0.66±0.14| 0.62±0.17| 0.06     | −0.04±0.16 | −0.07 to 0.00 | 0.32 68  |
| P>0.36 in two recordings (n=145) | 0.40±0.13| 0.40±0.13| 0.95     | −0.00±0.12 | −0.02 to 0.02 | 0.24 44  |
| P<0.36 and ≥0.36 (n=78)         | 0.43±0.15| 0.59±0.19| <0.0001  | 0.16±0.18  | 0.10 to 0.22 | 0.36 50  |
| P<0.36 and ≥0.36 (n=42)         | 0.60±0.09| 0.42±0.13| <0.0001  | −0.18±0.17 | −0.23 to −0.13 | 0.32 55  |

Gosse et al. [25] evaluated the reproducibility of QKD100–60 and AASI in 38 volunteers, who were selected from a cohort of 469 patients and who underwent repeat ambulatory recordings within 2 weeks. According to the French group [25], QKD100–60 (mean=224 ms; coefficient of variation=4%) had a better reproducibility than AASI (mean=0.60; coefficient of variation=25%). Coefficient of variation is the SD of the differences between paired measurements (SDD) divided by the mean of all measurements. The coefficient of variation does not account for the possible range of biological variation in the two ambulatory measures of arterial stiffness. We, therefore, expressed repeatability (twice SDD) as a percentage of near maximal variation in the measurements as given by four times the SD. Had the French investigators [25] expressed reproducibility in this way with the application of a proper test statistic, their results and conclusions could possibly have been different.

Matsui et al. [26] studied the reproducibility of the brachial-ankle pulse wave velocity (baPWV) and the carotid augmentation index (cAIX) in 103 hypertensive patients. The interval between the repeat measurements was 4 weeks. They measured baPWV, using a volumeplethysmographic device with four cuffs fitted with oscillometric sensors, which were wrapped around the upper arms and ankles and automatically and simultaneously inflated. The measurement of cAIX was done by multielement applanation tonometry. The Japanese investigators used the correlation between paired measurements as index of agreement [26]. The correlation coefficients were 0.89 for abPWV and 0.87 for cAIX. In our study, the correlation coefficients for AASI ranged from 0.52 to 0.61. In the absence of statistics
specifically designed to assess repeatability [26], the Japanese results are difficult to interpret. Moreover, the Japanese study was done under highly standardized laboratory conditions, using a fully automated technique, whereas we measured AASI over 24 h during the usual daily activities of our patients.

In our current study, we found that the differences between repeat minus first AASI correlated inversely with the differences in the night-to-day ratios of diastolic BP. Two recent reports already reported on AASI’s dependency on the nocturnal BP fall [27,28]. We also confirmed the inverse association between AASI and the night-to-day BP ratio in 1325 hypertensive patients referred to the Nijmegen clinic for ambulatory BP monitoring [29]. Several investigators demonstrated poor reproducibility of dipping status in hypertensive patients. Hernandez-del Rey [30] performed repeat ambulatory monitoring on 2 consecutive days and noticed that of 611 patients 147 (24.1%) participants switched from a nighttime dipper to nondipper or vice versa. Other studies [31] reported similar findings. When we stratified our study sample according to the consistency of dipping status, the repeatability coefficients expressed as a percentage of maximal variation were not substantially different. Thus, although there is a significant inverse association between AASI and the night-to-day BP ratio, this relation does not affect intra-individual repeatability of AASI to a large extent in stratified analyses.

In the present analysis, differences in the goodness of fit of the AASI regression line had an impact on the repeatability of AASI. Similar to recent observations by Gavish et al. [32], we demonstrated in 7604 participants enrolled in the International Database on Ambulatory BP monitoring in relation to Cardiovascular Outcomes (IDACO [33]) that the association of AASI with four main determinants of arterial stiffness (age, height, 24-h mean arterial pressure and 24-h heart rate) increased curvilinearly with the goodness of fit of the AASI regression line with most of the improvement in these associations occurring when the r2 of the AASI regression line was 0.36 or higher. In line with these still unpublished observations, the repeatability of AASI was 68% and 44% in patients who in repeat recordings consistently had an r2, respectively, below or above this 0.36 threshold.

The results of our study have to be interpreted in the context of its potential limitations. First, the Nijmegen cohort included 11.8% who were on antihypertensive medications. However, treatment remained unchanged between the first and repeat recording. Second, we did not standardize the ambulatory BP recordings across centres in terms of device type and intervals between readings. However, within patients, we used the same monitor and intervals in the first and repeat recordings. Moreover, we did not find any significant differences in repeatability between the five device types or between oscillometric versus auscultatory machines. To minimize heterogeneity, we additionally used the same programme to compute BP means and used time-weighted and robust regression.

In conclusion, estimates of group mean AASI were not different between repeat recordings. Within individual participants, the repeatability coefficients of AASI expressed as a percentage of near maximum variation were within the 50–60% range. These findings were consistent in older patients with isolated systolic hypertension and in a younger patient group with predominantly mixed hypertension. To our knowledge, this study is the first to report on the repeatability of AASI in hypertensive patients.
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References


Part 3

Procession of blood pressure: The Ambulatory Arterial Stiffness Index

Chapter 4.3: Correspondence

Putting a spin on the ambulatory arterial stiffness index.

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Putting a spin on the ambulatory arterial stiffness index

We defined the ambulatory arterial stiffness index (AASI) as unity minus the slope of diastolic on systolic blood pressure [1,2]. When determined from 24-h ambulatory blood pressure recordings, AASI reflects the dynamic relation between diastolic and systolic blood pressure throughout the day [1]. According to physiological concepts already proposed in 1914 [3], the stiffer the arterial tree, the closer the regression slope and AASI are to zero and one, respectively.

Since our original publications [1,2], several investigators have published on AASI. In the February issue of the Journal of Hypertension two articles [4,5] and one editorial comment [6] addressed the merits and limitations of AASI as a simple surrogate measure of arterial stiffness. Gavish and colleagues [4] proposed the use of the so-called symmetrical regression instead of ordinary regression to compute AASI. Baumann and colleagues [5] misread our publications [1,2] and computed AASI from the regression slope of systolic on diastolic blood pressure.

The study by Gavish et al. [4] included a selected group of 140 referred hypertensive patients, of whom 76 (54.3%) were on antihypertensive drug treatment. The study by Baumann et al. [5] included 106 potential kidney donors, of whom 31 were hypertensive (29.2%), and 22 (20.8%) were treated. The small sample size, selection, and the use of antihypertensive drugs make a reasonable interpretation of the results impossible. Our original publications derived conclusions from a considerably larger sample size and included a randomly selected Chinese population (n=348 [1]) and untreated hypertensive patients (n=11291 [2]).

Both publications [4,5] also built part of their argument on the correlation of AASI with pulse pressure. These associations are spurious because the dependent and independent variables are both calculated from the same systolic and diastolic blood pressure readings. Nevertheless, while keeping this potential flaw in mind, in our Belgian cohort (n=552 [7]), the correlation with pulse pressure was stronger for AASI than for symmetrical AASI (0.50 vs 0.17; P<0.001). Moreover, the correlation between AASI and pulse pressure was almost identical in 428 diastolic dippers and 124 diastolic nondippers (0.44 vs. 0.44; P¼0.98).

Baumann and co-workers [5] only had about 19 nondippers to investigate these associations.

The studies by Gavish et al. [4] and Baumann et al. [5] spin an issue first raised by Schillaci and co-workers [8], and subsequently confirmed by us [9], that AASI is inversely correlated with night-time dipping. According to the experts [10], aortic pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness. In 166 Chinese volunteers [1], in whom we measured AASI and PWV within 24 h, the correlation coefficients with the percentage fall in nocturnal blood pressure were similar for PWV and AASI [MTEST statement in the PROC REG procedure of the SAS package, version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA); P>0.54], amounting to −0.54 and −0.49 for systolic dipping and to −0.56 and −0.57 for diastolic dipping. Moreover, AASI was consistently and significantly related to PWV in 99 diastolic dippers (r=0.27; P=0.007) as well as in 67 diastolic nondippers (r=0.41; P=0.0005).

We concur with our colleagues [6,10] that AASI is an indirect measure of arterial stiffness and must be under the influence of other haemodynamic factors such as heart rate and the velocity of left ventricular ejection. However, we strongly believe that with regard to AASI, researchers should now leave the circular argumentation and the mathematical hair-splitting. What clinically counts at the end of the line is that AASI improves the risk stratification based
on ambulatory blood pressure monitoring. To date, several cross-sectional studies [11,12] and at least three prospective cohort studies [2,13,14] have demonstrated the association of AASI with either the signs of target organ damage in never-treated hypertensive patients [11] or the incidence of cardiovascular mortality and morbidity [2,13,14]. When adjusted for pulse pressure [2,13,14] or PWV [15], AASI remained predictive, in particular of stroke.

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Reply

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The authors point in their comment to the fact that we computed ambulatory arterial stiffness index (AASI) based on the regression slope of systolic–diastolic blood pressure. If we computed our data according to the original work of Li et al. [1] and Dolan et al. [2], the correlation between diastolic dipping and AASI remained significant (r=−0.28; P=0.006). Moreover, the difference between nondipper and dipper with respect to AASI remained significant (mean±SD; nondipper, 0.36±0.14; dipper, 0.29±0.11; P=0.01).

Another point made by the authors was the heterogeneity of our group including normotensive and hypertensive subjects. Therefore, we computed our data according to the original work of Li et al. [1] and Dolan et al. [2], excluding our 31 hypertensive individuals. Again, the correlation between diastolic dipping and AASI remained significant; however, to a lesser extent (r=−0.23; P=0.03). Moreover, the difference between nondipper and dipper with respect to AASI remained significant for the normotensive cohort (mean±SD; nondipper, 0.35±0.15; dipper, 0.29±0.11; P=0.04). Therefore, our data are in line with the work of several groups including the authors [3].

Schillaci et al. [4] pointed out hemodynamic factors potentially influencing AASI. Similarly, our discussion focused on the potential role of autonomic nerve function as a cause of dipping [5] and thus as factor influencing AASI. We believe that understanding factors influencing AASI, such as the autonomic nerve function, may be useful for the further interpretation of AASI, as we fully agree with the authors that AASI improves the risk stratification based on ambulatory blood pressure monitoring.

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We would like to thank the authors for their interest in the topic of our article.

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We concur with Adiyaman et al. [1] that the ultimate testing ground for ambulatory arterial stiffness index (AASI), as for any newly proposed index of target organ damage, is represented by its ability to predict cardiovascular complications over and above the prognostic power of established risk factors and markers of organ damage. In this regard, several of the authors of the study by Adiyaman et al. should be commended for their tremendous amount of work aimed at elucidating the prognostic contribution of AASI as well as its limitations [2–5]. Overall, in different clinical settings, AASI was found to be an independent predictor of stroke [2–4] and cardiovascular mortality [2,3] but not of cardiovascular events [5] and coronary heart disease [3,5].

On the contrary, we are certain that Adiyaman et al. will agree with our view that the actual physiological significance of AASI is far from being clarified [6]. Recently published data [7] confirm our finding [8] that, at least in hypertensive individuals, AASI may not be considered as a surrogate marker of arterial stiffness. In 515 volunteers examined by us [8,9] and in 824 individuals observed by Jerrard-Dunne et al. [7], the positive correlation between AASI and carotid-femoral pulse-wave velocity, which is considered as a direct measure of aortic stiffness, was considerably weaker than that reported earlier in a smaller cohort of 166 predominantly normotensive Chinese individuals [10] and was lost following adjustment for age [7–9]. Overall, AASI was found to be a poor predictor of aortic pulse-wave velocity, with 95% prediction limits for the AASI to predict pulse-wave velocity as wide as ±4.18 m/s [7].

We had previously shown that this lack of association between AASI and established, though indirect, measures of arterial stiffness might be in part related to the strong, spurious inverse association between AASI and day–night diastolic, and consequently systolic, blood pressure (BP) reduction [8]. It has been suggested that such a strong relation may be due to the fact that nocturnal BP fall might be in itself a correlate of arterial stiffness [1]. However, the absence of a significant relationship between nocturnal BP fall and aortic pulse-wave velocity in two large, independent studies on hypertensive individuals [7,8] makes this hypothesis unlikely. The paper by Gavish et al. [11] is a first attempt to eliminate the limitations characterizing such artefactual relationship by using a symmetrical regression model.

In conclusion, the development of AASI [2,10] unquestionably represents a theoretically attractive means of easily exploring arterial stiffness without the use of dedicated, operator-dependent equipment. However, given the present uncertainties regarding the meaning and the clinical importance of AASI, we believe that any contribution toward a better understanding of AASI should not be considered as a pedant hair-splitting exercise but as an attempt to more deeply appreciate the mechanisms and the clinical significance of the dynamic features characterizing the relation between systolic and diastolic BPs.
References


Reply

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The possibility that the observed linear relationship between repeatedly measured systolic and diastolic blood pressures can provide parameters that express mechanical properties of arteries and have clinical significance is exciting. Schillaci and Parati [1] expressed the increasing interest in this phenomenon by devoting an editorial to two articles on this topic [2,3]. This correspondence is a response to the letter by Staessen and colleagues, who addressed these publications [1–3]. We raise basic questions related to definition, determination and physiological origins of selected parameters in an attempt to widen the interest in this newly emerging topic, beyond arterial stiffness index (AASI) and arterial stiffness.

Parameter definition and determination
The linear relationship between variations in systolic and diastolic pressures over time is known for office measurements with follow-up over years in the Framingham study [4]; 24-h ambulatory measurements [5–7] and can be clearly demonstrated in home measurements over months and in beat-by-beat measurements within few minutes. Therefore, this phenomenon is not limited to ambulatory blood pressure measurements, suggesting that the dipping status may be important mainly as a generator of variability range, as already pointed out by Schillaci et al. [8]. The relevant parameter is the slope of the regression line associated with either systolic versus diastolic plot (‘S–D slope’) or with diastolic versus systolic plot (‘D–S slope’), where AASI is defined by 1_[D–S slope]. The S–D and D–S slopes are reciprocal to each other when calculated by symmetric regression (but not with standard regression) [2] and can be referred collectively as ‘slope’. The importance of using appropriate regression procedure for ‘slope’ determination cannot be underestimated when correlations with clinical and demographic variables are found to depend strongly on the regression method applied.

‘Slope’ determination
by standard regression, as commonly used, leads to flattening of a strong dependence on age and generates a negative correlation between AASI and systolic dipping, as observed by Schillaci et al. [8] and Bauman et al. [3]. This correlation turns weak and positive upon using symmetric regression [2]. The underlying intriguing phenomenon is the observed relationship between systolic–diastolic correlation coefficient r and systolic or diastolic dipping [2]. In fact, neither AASI nor S–D slope were found to depend on r when determined by symmetric regression [2].

Underlying physiological principles
Real arteries cannot be described as simple elastic tubes characterized by a single value of arterial stiffness. Instead, arterial stiffness increases for greater pressure. This ‘arterial-stiffening’ property that sharply increases after age 50–60 years reflects the nonlinear pressure–diameter (or volume) relationship [9]. As a result, arterial stiffness, as well as pulse-wave velocity, may undergo large variations between systolic and diastolic pressures during the cardiac cycle [10,11] and both are expected to decrease with nocturnal blood pressure fall. In contrast, ‘slope’ is by definition a parameter that is independent of pressure over the entire
pressure range. The fact that ‘slope’ measured by 24-h ambulatory blood pressure monitoring displayed independence of mean arterial pressure in a tested population of 140 patients [2] casts further doubts about the justification of associating AASI with arterial stiffness, in spite of its observed correlation with pulse-wave velocity [6,8].

The possibility that the ‘slope’ expresses the arterial stiffening during the cardiac cycle and not arterial stiffness is challenging. Support for this view comes from a theoretical derivation by Gavish [12] showing that S–D slope expresses quantitatively the relative increase of arterial stiffness during the systole that appears independent of pressure [2], as well as from important work by Conway and Smith [13] and Abboud and Huston [14] that attempted to characterize arterial stiffening by a parameter called ‘arterial rigidity index’. These researchers measured beat-to-beat intra-arterial pressure in response to inhalation of amyl nitrite. This parameter increased with age and showed good potential as an index for arterial aging and degenerative vascular disease. Arterial stiffening was found to reflect increased loading of the collagen tissue in the vascular wall [15]. Increased collagen/elastin ratio that characterizes vascular aging and pathology may lead to increase in both stiffness and stiffening. This pressure-independent structural aspect may explain why AASI positively correlates with pulse wave velocity and expresses arterial stiffening but not stiffness. The present view is consistent with the finding of Dolan et al. [7] that AASI is a predictor of cardiovascular mortality in hypertensive patients.

In conclusion, in searching for the clinical significance and the physiological origin of the linear relationship between systolic and diastolic pressures, it is necessary to expand the view beyond ambulatory blood pressure measurements and arterial stiffness. The possibility of characterizing the nonlinear mechanical properties of arteries using pressure-independent parameters derived from blood pressure measurements is stimulating.

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Part 3

Procession of blood pressure: The Ambulatory Arterial Stiffness Index

Chapter 4.3: Correspondence

Dipping Deeper Into the Ambulatory Arterial Stiffness Index

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Dipping Deeper Into the Ambulatory Arterial Stiffness Index

To the Editor:
Methodologic and conceptual issues seriously weaken the conclusions of Schillaci et al1 on the ambulatory arterial stiffness index (AASI), as published in the May 2007 issue of Hypertension.

Schillaci et al1 reported that, in 515 untreated patients, AASI depended on the nocturnal blood pressure fall. We confirmed this observation in our Flemish population study2. The correlation coefficients were similar to those in the report by Schillaci et al1: −0.24 versus −0.28 for systolic blood pressure (2-sided \( P \) value computed by Fisher’s \( Z \) transformation, 0.42), and −0.39 versus −0.46 for diastolic blood pressure (\( P=0.11 \)). However, the ambulatory recording of 1 of the representative patients of Schillaci et al1 included \( \approx 25 \) nighttime and \( \approx 35 \) daytime readings. The night:day ratio of the number of blood pressure readings was therefore 0.71, whereas in our studies,2,3 it was \( \approx 0.30 \). As shown in the Figure, this ratio influences estimates of AASI. Furthermore, in our 166 Chinese volunteers,3 in whom we measured AASI and pulse wave velocity (PWV) within 24 hours, the correlation coefficients with the percentage fall in nocturnal blood pressure were similar for PWV and AASI (MTEST statement in the PROC REG procedure of the SAS package, version 9.1.3; \( P>0.54 \)), amounting to −0.54 and −0.49 for systolic dipping and to −0.56 and −0.57 for diastolic dipping.

Schillaci et al1 did not seek survival of AASI in the multivariate-adjusted association with left ventricular mass index. In Table 3 of their report,1 they introduced not independent but highly intercorrelated predictors, bound to remove AASI from the model. The correlation between the daytime systolic pressure and the nocturnal fall in systolic blood pressure is close, because computation of the latter requires use of the former. Schillaci et al1 did not report the \( t \)-to-enter for AASI and the variable, probably the daytime systolic blood pressure, that excluded AASI to remain in the model. More importantly, Schillaci et al1 failed to demonstrate that, with similar adjustments applied as for AASI, the association between left ventricular mass index and PWV remained significant.

In line with our first report on AASI,3 Schillaci et al1 found significant (\( P<0.001 \)) association between PWV and AASI, although the correlation coefficient was lower (0.28 versus 0.51; \( P=0.0039 \)). Schillaci et al1 must be aware of Bland and Altman’s4 recommendations for assessing concordance between 2 measurements and our analyses complying with these recommendations.5 Nevertheless, the Italian investigators did not go beyond reporting a correlation coefficient as measure of agreement. Moreover, it is conceptually wrong in the assessment of concordance between measurements to adjust for common determinants underlying the measured trait. In our Chinese volunteers,3 mean arterial pressure removed the association between PWV and AASI. That accounting for common determinants weakens the correlation between PWV and AASI actually corroborates that these 2 measurements reflect arterial stiffness.

In conclusion, we confirmed that AASI is inversely correlated with the nocturnal fall in blood pressure, especially in ambulatory recordings with a disproportionately large number of nighttime readings. We concur with the idea that AASI is an indirect measure of arterial stiffness.3,5 However, we disagree with inappropriate or unnecessary adjustment in regression models,1 and we regret that the information on the correlations of left ventricular mass index with AASI and PWV was incomplete.1
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Disclosures
None.

References
Response to Dipping Deeper Into the Ambulatory Arterial Stiffness Index

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Although we regret that Adiyaman et al1 misinterpreted some of our results, we are glad to see that they agree with the main findings of our study,2 in which we described a strong and previously undetected inverse association between ambulatory arterial stiffness index (AASI) and day-night blood pressure (BP) fall. Indeed, they were able to replicate our findings in 2 different cohorts.3,4

Adiyaman et al1 argue that the estimate of AASI may be influenced by the night:day ratio of the number of BP readings. However, to support their view, they rely on ambulatory BP recordings performed with a very low frequency of nocturnal BP readings. In fact, the night:day ratio of the number of BP readings in their study was only ≈0.30 with 26 to 30 measurements during the day and 8 to 9 measurements at night (see the figure in the letter by Adiyaman et al1) because of a longer nocturnal interval between automated measurements. In our representative patients (Figure 3 of our article),2 the number of valid BP measurements was 34 during nighttime and 57 during daytime (and not ≈25 and ≈35, as erroneously indicated by Adiyaman et al1). Such a distribution, rather than including a “disproportionally large” number of nocturnal readings, is the desirable result of having BP evenly measured every 15 minutes throughout the 24 hours. By avoiding an artificially lower BP sampling frequency at night than during the day, in our article the night:day ratio in the number of BP readings simply mirrors the physiologically different duration of the nighttime and daytime subperiods.

Our demonstration that day-night BP reduction is a major determinant of AASI provides a rational explanation for the dependency of AASI on the number of diurnal and nocturnal readings. Given that nocturnal diastolic and systolic BP reductions are strongly related to each other, the physiological nocturnal BP fall generates a number of nocturnal systolic and diastolic BP values, which are considerably lower than the corresponding daytime values. This, in turn, increases the regression coefficient of diastolic BP on systolic BP (B) and reduces AASI. If the number of nocturnal readings is artificially reduced by adopting longer betweenmeasurement intervals at night, this reduces B and increases AASI. As a matter of fact, in our cohort, AASI calculated on the basis of daytime readings, thus excluding the nocturnal values, was much higher than 24-hour AASI (0.48±0.26 versus 0.31±0.17). In other words, we postulate that a low number of nocturnal readings artificially increases AASI, irrespective of any association with an increase in arterial stiffness.

Another point raised by Adiyaman et al1 is the high intercorrelation between daytime systolic BP and nocturnal fall in systolic BP, which should prevent these variables from being include
simultaneously in a multivariate model. This observation is incorrectly made with reference to our study, however, in which we included in the same model daytime BP and percentage of nocturnal BP fall. In our population, there was indeed no significant correlation between the 2 variables ($r=0.07 \; P=0.08$), and the examined model was found to be free from collinearity using standard diagnostic techniques (tolerance: 0.89 to 0.99).

Moreover, Adiyaman et al argue that information on the correlation between left ventricular mass and pulse wave velocity was incomplete in our article. Indeed, it was completely absent. We did not address the association between pulse wave velocity and left ventricular mass index simply because this was not the aim of our study. Our observations focused on what was the primary target of our study, ie, the actual meaning of AASI. The important result of our article was that the previously reported association with a common index of organ damage, such as left ventricular mass, depends on the shared association with the degree of nocturnal BP reduction.

We agree that Bland-Altman plots may give a different and complementary view of the concordance between 2 measures, in particular when comparing 2 estimates of the same parameter. Conversely, we disagree that a Bland-Altman plot could be helpful to assess concordance between AASI and aortic pulse wave velocity. These 2 parameters measure quite different biological traits, which are distributed over different numerical ranges. Because data of different kind cannot be averaged or subtracted, absolute values of means, differences, and coefficients of variation cannot be given in such nondimensional graphs (see Figure 3, panel 3, in the article by Li et al).

Finally, we do not agree with Adiyaman et al that adjustment for common determinants is inappropriate when assessing concordance between a newly proposed and an established trait. At least, the confounding effect of age should be taken into account when assessing the clinical value of any new surrogate marker of atherosclerosis. In our population, the bivariate relation between AASI and aortic pulse wave velocity ($r=0.28 \; P<0.001$) lost its significance when the effect of age was taken into account (partial $r=0.05 \; P=0.39$), not even considering the impact of mean arterial pressure and other variables. Although the actual physiological significance of AASI needs to be elucidated further, these data confirm our view that, at least in untreated hypertensive subjects, AASI may not be considered as a surrogate marker of arterial stiffness tout court.

**Disclosures**

None.

**References**


Part 3

Procession of blood pressure: The Ambulatory Arterial Stiffness Index

Chapter 4.4

Determinants of the Ambulatory Arterial Stiffness Index in 7604 Subjects From 6 Populations.

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Abstract—The ambulatory arterial stiffness index (AASI) is derived from 24-hour ambulatory blood pressure recordings. We investigated whether the goodness-of-fit of the AASI regression line in individual subjects ($r^2$) impacts on the association of AASI with established determinants of the relation between diastolic and systolic blood pressures. We constructed the International Database on the Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (7604 participants from 6 countries). AASI was unity minus the regression slope of diastolic on systolic blood pressure in individual 24-hour ambulatory recordings. AASI correlated positively with age and 24-hour mean arterial pressure and negatively with body height and 24-hour heart rate. The single correlation coefficients and the mutually adjusted partial regression coefficients of AASI with age, height, 24-hour mean pressure, and 24-hour heart rate increased from the lowest to the highest quartile of $r^2$. These findings were consistent in dippers and nondippers (night:day ratio of systolic pressure $\geq 0.90$), women and men, and in Europeans, Asians, and South Americans. The cumulative $z$ score for the association of AASI with these determinants of the relation between diastolic and systolic blood pressures increased curvilinearly with $r^2$, with most of the improvement in the association occurring above the 20th percentile of $r^2$ (0.36). In conclusion, a better fit of the AASI regression line enhances the statistical power of analyses involving AASI as marker of arterial stiffness. An $r^2$ value of 0.36 might be a threshold in sensitivity analyses to improve the stratification of cardiovascular risk.
In 1914, MacWilliam and Melvin already noticed that loss of elasticity in the arterial system impacted on the relation of diastolic with systolic pressure. We recently defined the ambulatory arterial stiffness index (AASI) as unity minus the regression slope of diastolic on systolic blood pressure in individual 24-hour ambulatory blood pressure recordings. The stiffer the arterial tree, the closer the regression slope and AASI are to 0 and 1, respectively. We validated AASI against other markers of arterial stiffness, such as the systolic augmentation index and aortic pulse wave velocity. In spite of the prognostic accuracy of AASI over and beyond classical risk factors, including pulse pressure and pulse wave velocity, some researchers criticized AASI. It would be a surrogate marker of arterial stiffness not different from pulse pressure. Schillaci et al reported that AASI decreased with less nocturnal dipping in blood pressure. Gavish et al suggested that symmetrical regression might provide a better estimate of AASI less affected by the nocturnal blood pressure fall and the goodness-of-fit of the regression slope, as expressed by the coefficient of determination \( r^2 \). To clarify these issues, we analyzed the International Database on the Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes. We investigated whether \( r^2 \) affects the association of AASI with established determinants of the relation between diastolic and systolic blood pressures, including age, body height, heart rate, and mean arterial pressure. We evaluated the consistency of the determinants of AASI in dippers and nondippers, women and men, and across different ethnic groups.

Methods

Study Population
Previous publications (for details, see the expanded Methods in the online data supplement, available at http://hyper.ahajournals.org) described the construction of the International Database on the Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes. All of the included studies received ethical approval. The current analysis incorporates the baseline data of 2138 residents from Copenhagen, Denmark; 1127 subjects from Noorderkempen, Belgium; 1100 older men from Uppsala, Sweden; 1520 inhabitants from Ohasama, Japan; 349 villagers from the JingNing county, China; and 1370 subjects from Montevideo, Uruguay. All 7604 subjects were ≥18 years old, gave informed written consent, and had ≥30 daytime and ≥5 nighttime blood pressure readings.

Blood Pressure Measurement
We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day, or at intervals ranging from 1514 to 3015 minutes during daytime and from 30 [14] to 60 [15] minutes at night. The devices implemented an auscultatory algorithm (Accutracker II) in Uppsala or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM-630) in the other cohorts. We used linear regression, weighted by the time interval between successive readings, to determine the regression slope of diastolic on systolic blood pressure in individual recordings. AASI was unity minus the regression slope. Pulse pressure was systolic minus diastolic blood pressure. Because the oscillometrically measured mean arterial pressure was not available in all of the cohorts, we computed mean arterial pressure as diastolic blood pressure plus one third of pulse pressure. We studied the concordance between the computed and the oscillometrically measured mean arterial pressures in 1144 Belgian and 349 Chinese participants. Ambulatory hypertension was a 24-hour blood pressure of 130 mm Hg systolic or 80 mm Hg diastolic or higher or the use of antihypertensive drugs. While accounting for the daily pattern of activities of the participants, we
defined daytime as the interval from 10 AM to 8 PM in Europeans12,14,15 and South Americans17 and from 8 AM to 6 PM in Asians.13,16 The corresponding nighttime intervals ranged from midnight to 6 AM12,14,15,17 and from 10 PM to 4 AM,13,16 respectively. In dichotomous analyses, we defined nondipping as a night:day ratio of systolic blood pressure of ≥0.90 [19].

Other Measurements
We used the questionnaires originally administered in each cohort12–17 to obtain information on each subject’s medical history and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or ≥11.1 mmol/L (200 mg/dL),20 respectively, or the use of antidiabetic drugs.

Statistical Analyses
For database management and statistical analyses, we used SAS 9.1.3 (SAS Institute) and its JMP add-on, version 6.0. We checked that the assumption of normality was applicable to the variables under study by normal probability plots. We compared means and proportions by the large sample z test and by the χ2 statistic, respectively. Statistical significance was a 2-sided P value of 0.05. In single and multiple regression analyses, the established determinants of the relation of diastolic on systolic blood pressure were age, body height, 24-hour mean arterial pressure, and 24-hour heart rate.2 In single regression analysis, we also considered the night:day ratio of systolic blood pressure8,21 and 24-hour pulse pressure.22 Multivariable-adjusted models included as covariates cohort and/or sex, as appropriate, and age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. In sensitivity analyses, we additionally adjusted for serum cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiovascular disease. We used the coefficient of determination (r2) as a measure of the goodness-of-fit (Figure 1) of the regression line of diastolic on systolic blood pressure in individual ambulatory recordings. We subdivided the study population in cohort and sex-specific quartiles of r2. We compared Pearson’s correlation coefficients and partial regression coefficients.
of AASI with its determinants, using Fisher’s $z$ transform and interaction terms with binary variables coding for the quartiles of $r^2$, respectively. In the last step of the analyses, we computed a cumulative $z$ score for the single correlation coefficients of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. We plotted the average cumulative $z$ score against the goodness-of-fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (≈90th percentile of $r^2$) by steps of 0.01.

Results

Characteristics of Participants
The 7604 participants included 4365 Europeans (57.4%), 1869 Asians (24.6%), and 1370 South Americans (18.0%). Of the 7604 participants, 3472 were women (45.7%), 1703 (22.4%) were taking blood pressure–lowering drugs, and 946 (12.4%) had ambulatory hypertension. Mean±SD age was 56.9±13.9 years. At enrollment, 2203 participants (29.0%) were current smokers, and 3535 (46.5%) reported intake of alcohol. In the whole study population, the 24-hour blood pressure averaged 124.8±14.4 mm Hg systolic and 73.9±9.2 mm Hg diastolic. The systolic and diastolic daytime levels averaged 131.2±15.5 mm Hg and 78.9±9.3 mm Hg, and the nighttime blood pressures were 113.2±15.5 mm Hg and 65.0±9.2 mm Hg. The night:day ratio of systolic blood pressure was 0.87±0.08.

The 24-hour mean arterial pressure averaged 90.0±9.7 mm Hg. In 1493 subjects with available data, the computed compared with the measured mean arterial pressure (SD) was 0.71±2.50 mm Hg higher (88.3±9.1 versus 87.6±9.4 mm Hg; $P<0.0001$). The slope ($P=0.87$) and the intercept ($P=0.54$) of the regression line of the measured on the computed mean arterial pressure ($r=0.98$; $P<0.0001$) did not differ from the parameters of the line of identity (Figure S1).

In all of the subjects, AASI averaged 0.46±0.18 and 24-hour pulse pressure 50.9±10.1 mm Hg. Mean $r^2$ in 7604 individual recordings was 0.54±0.20. $r^2$ was lower in the auscultatory recordings in 1100 older Swedish men than in the oscillometric registrations in 6504 other subjects (0.42±0.20 versus 0.56±0.19; $P<0.001$). Table 1 shows the characteristics of the participants by quartiles of $r^2$. All of the $P$ values for the differences between quartiles were significant ($P≤0.01$), with the exception of diastolic blood pressure ($P=0.09$).

Unadjusted Analyses
In all of the subjects combined, in single regression analysis, AASI correlated positively with age and 24-hour mean arterial pressure and negatively with height and 24-hour heart rate (Table 2). As shown in Table 2 and Figure 2, the correlation coefficients of AASI with age, height, 24-hour mean arterial pressure, and 24-hour heart rate were significantly tighter in the highest compared with the lowest quartile of $r^2$. Figure 3 shows the plot of cumulative $z$ scores of the aforementioned 4 covariables against the goodness-of-fit of the AASI regression line in steps of 0.01 of $r^2$, going from 0 to 0.80. The first, fifth, 10th, 20th, 50th, 75th, and 90th percentile values of $r^2$ were 0.05, 0.17, 0.25, 0.36, 0.56, 0.69, and 0.79, respectively.

The association between AASI and 24-hour pulse pressure increased across the quartiles of $r^2$ and was 0.49 ($P<0.0001$) in the whole study population. The correlation between AASI and serum cholesterol did not increase with $r^2$. In all of the subjects combined, the correlation coefficient between AASI and the night:day ratio in systolic blood pressure was 0.15 ($P<0.001$).
This association was inconsistent across the quartiles of $r^2$ (Table 2). The positive correlation between AASI and the systolic night:day ratio was larger in 1100 auscultatory recordings than in 6504 oscillometric registrations (0.28 versus 0.15; $P<0.0001$). Furthermore, of 7604 participants, 5361 were dippers (70.5%) and 2243 were nondippers (29.5%). The associations of AASI with age, body height, and 24-hour heart rate and mean arterial pressure were similar in dippers and nondippers (Figure 2).

**Multivariable Analyses**
In all 7604 of the subjects combined, AASI increased independently with age and 24-hour mean arterial pressure and decreased with height and 24-hour heart rate (Table 3). The multivariable-adjusted associations of AASI with age, 24-hour mean arterial pressure, and 24-hour heart rate were significantly closer in the highest compared with the lowest quartile (Table 3). In multiple regression, the variance of AASI explained ($R^2$) by age, height, 24-hour mean arterial pressure, and 24-hour heart rate increased from 0.04 to 0.37 from the lowest to the highest quartile of $r^2$.

**Sensitivity Analyses**
The aforementioned unadjusted (Table S1) and multivariable-adjusted (Table S2) findings were consistent in women and men and in Europeans, Asians, and Americans (see online Data Supplement). Analyses, from which we excluded the 1100 auscultatory recordings, also produced consistent results (Tables S3 and S4 and Figure S2). Our findings also remained consistent after the additional adjustment of the results in Table 3 for serum cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiovascular disease (data not shown).

**Discussion**
We investigated whether $r^2$ affects the association of AASI with established determinants of the relation between diastolic and systolic blood pressures. We confirmed that the strength of the relation of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate increased with the goodness-of-fit of the AASI regression line. In fact, in the lowest quartile of the fit, the correlations of AASI with these determinants were weak and at times inconsistent with the expected direction of the associations.
Table 1. Baseline Characteristics of Participants by Categories of the Goodness-of-Fit of AASI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low</th>
<th>Medium-Low</th>
<th>Medium-High</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limits of goodness-of-fit, $r^2$</td>
<td>&lt;0.40</td>
<td>0.40 to 0.55</td>
<td>0.55 to 0.70</td>
<td>≥0.70</td>
</tr>
<tr>
<td>Total, n</td>
<td>1901</td>
<td>1906</td>
<td>1896</td>
<td>1901</td>
</tr>
<tr>
<td>Auscultatory recordings</td>
<td>492 (25.9)</td>
<td>337 (17.7)</td>
<td>196 (10.5)</td>
<td>75 (3.9)</td>
</tr>
<tr>
<td>European</td>
<td>1376 (72.4)</td>
<td>1284 (67.4)</td>
<td>1066 (66.2)</td>
<td>639 (33.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>134 (7.0)</td>
<td>248 (13.0)</td>
<td>457 (24.1)</td>
<td>1030 (54.2)</td>
</tr>
<tr>
<td>South American</td>
<td>361 (20.6)</td>
<td>374 (19.6)</td>
<td>373 (19.7)</td>
<td>232 (12.2)</td>
</tr>
<tr>
<td>Women</td>
<td>759 (39.9)</td>
<td>818 (42.9)</td>
<td>871 (45.8)</td>
<td>1024 (53.8)</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>444 (23.7)</td>
<td>367 (19.3)</td>
<td>375 (19.8)</td>
<td>517 (27.2)</td>
</tr>
<tr>
<td>Smokers</td>
<td>503 (26.7)</td>
<td>597 (31.5)</td>
<td>586 (31.0)</td>
<td>518 (27.3)</td>
</tr>
<tr>
<td>Using alcohol</td>
<td>1022 (53.8)</td>
<td>1001 (52.5)</td>
<td>879 (46.4)</td>
<td>633 (33.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>150 (7.9)</td>
<td>117 (6.1)</td>
<td>120 (6.3)</td>
<td>181 (9.5)</td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td>266 (14.0)</td>
<td>250 (13.1)</td>
<td>208 (11.0)</td>
<td>182 (8.5)</td>
</tr>
<tr>
<td>Nondippers for systolic pressure</td>
<td>952 (50.1)</td>
<td>585 (30.7)</td>
<td>419 (22.1)</td>
<td>287 (15.1)</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.8±13.6</td>
<td>57.0±14.0</td>
<td>55.4±13.9</td>
<td>55.5±13.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.2±10.3</td>
<td>167.0±10.7</td>
<td>165.4±11.5</td>
<td>159.9±12.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.4±15.1</td>
<td>72.3±15.2</td>
<td>70.0±16.1</td>
<td>63.6±15.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.2±4.3</td>
<td>25.8±4.1</td>
<td>25.4±4.1</td>
<td>24.6±3.8</td>
</tr>
<tr>
<td>24-h ambulatory measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>128.6±15.6</td>
<td>125.2±14.4</td>
<td>123.5±13.6</td>
<td>121.8±13.2</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>73.5±9.1</td>
<td>73.9±8.5</td>
<td>74.1±8.3</td>
<td>74.2±8.1</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>91.9±10.4</td>
<td>91.0±9.8</td>
<td>90.6±9.4</td>
<td>90.1±9.2</td>
</tr>
<tr>
<td>Systolic night/day ratio</td>
<td>0.908±0.086</td>
<td>0.867±0.076</td>
<td>0.853±0.076</td>
<td>0.832±0.079</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>55.0±11.1</td>
<td>51.3±9.8</td>
<td>49.4±9.2</td>
<td>47.8±8.5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71.4±8.5</td>
<td>72.6±9.4</td>
<td>72.3±9.0</td>
<td>71.5±8.7</td>
</tr>
<tr>
<td>AASI</td>
<td>0.63±0.15</td>
<td>0.47±0.13</td>
<td>0.38±0.13</td>
<td>0.33±0.14</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.9±1.1</td>
<td>5.8±1.2</td>
<td>5.6±1.1</td>
<td>5.4±1.0</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>5.3±1.5</td>
<td>5.2±1.3</td>
<td>5.1±1.1</td>
<td>5.0±1.0</td>
</tr>
</tbody>
</table>

Data are No. (%) or mean±SD, unless otherwise specified. Nondipping was a nighttime ratio of systolic blood pressure ≥0.90. All of the P values for the differences between quartiles were significant (P<0.01), with the exception of diastolic pressure (P=0.69).

Table 2. Correlates of AASI in the Whole Study Population and by Quartiles of the Goodness-of-Fit of AASI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartiles of the Goodness-of-Fit ($r^2$) of the AASI Regression Line</th>
<th>P vs Low Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Subjects</td>
<td>Low</td>
</tr>
<tr>
<td>No.</td>
<td>7604</td>
<td>1901</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit, $r^2$</td>
<td>0.54±0.20</td>
<td>0.26±0.10</td>
</tr>
<tr>
<td>AASI</td>
<td>0.46±0.18</td>
<td>0.63±0.15</td>
</tr>
<tr>
<td>Correlation coefficient of AASI with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.37‡</td>
<td>0.20‡</td>
</tr>
<tr>
<td>Body height</td>
<td>0.06‡</td>
<td>0.03</td>
</tr>
<tr>
<td>24-h mean arterial pressure</td>
<td>0.14‡</td>
<td>0.06‡</td>
</tr>
<tr>
<td>24-h heart rate</td>
<td>-0.17‡</td>
<td>-0.09‡</td>
</tr>
<tr>
<td>24-h pulse pressure</td>
<td>0.49‡</td>
<td>0.35‡</td>
</tr>
<tr>
<td>Systolic night/day ratio</td>
<td>0.15‡</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.11‡</td>
<td>0.06*</td>
</tr>
</tbody>
</table>

Significance of the correlation coefficients: *P<0.05; ‡P<0.01; ‡‡P<0.001.
Figure 2. Correlations of AASI with age, height (BH), 24-hour mean arterial pressure (MAP), and 24-hour heart rate (HR) across quartiles of the goodness-of-fit of the AASI regression line ($r^2$) in all 7604 subjects (A), 5391 dippers (B), and 2243 nondippers (C). $P$ values are for the differences between the bottom and top quartiles.

Figure 3. Plot of the average cumulative z score against the goodness-of-fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (=90th percentile of $r^2$) by steps of 0.01. The cumulative z score is the sum of the unsigned Fisher z transforms of the single correlations of AASI with age, body height, 24-hour mean arterial pressure, and 24-hour heart rate. Vertical lines denote percentiles of the distribution of the goodness-of-fit ($r^2$).
For our current analyses, we used established determinants of AASI. In 348 randomly recruited Chinese subjects, AASI significantly and independently increased with age and mean arterial pressure, decreased with body height, and was higher in women than in men. Most other studies reported differences of these characteristics across quantiles of the distribution of AASI. They showed more advanced age, a higher proportion of women, and elevated blood pressure in higher AASI quantiles. In keeping with several other studies, in our hands, AASI did not or only weakly correlate with serum cholesterol, body mass index, and smoking. AASI was negatively correlated with heart rate. Although heart rate is not a determinant of static arterial stiffness (pulse wave velocity), it is a determinant of dynamic measures of arterial stiffness, such as AASI or the augmentation index. A faster heart rate reduces the time required for the reflected pressure wave to reach the central arteries and leads to augmentation of systolic blood pressure. As reported by others, there was a positive correlation between AASI and pulse pressure, which increased with $r^2$. Using 24-hour ambulatory pulse pressure as an index of arterial stiffness assumes that the difference between diastolic and systolic blood pressure is constant throughout the day. In contrast, AASI accounts for the dynamic relation between diastolic and systolic blood pressures in individual 24-hour ambulatory recordings. Furthermore, in hypertensive patients and representative population samples, AASI predicted cardiovascular mortality and fatal and nonfatal stroke, over and beyond classic risk factors, including pulse pressure and even aortic pulse wave velocity. These prospective studies support the use of AASI for risk stratification.

Schillaci et al reported that, in 515 untreated patients, AASI depended on the nocturnal blood pressure fall. We confirmed this observation in our Flemish population study. The correlation coefficients were similar to those in the report by Schillaci et al: Flemish population versus Italian patients, −0.24 versus −0.28 for systolic blood pressure (2-sided $P$ value for difference computed by Fisher’s $z$ transformation: 0.42) and −0.39 versus −0.46 for diastolic blood pressure ($P=0.11$). In our current study, the correlation coefficient between AASI and the night:day ratio of systolic blood pressure ($n=7604$) was significantly weaker ($P=0.0013$) than in the hypertensive patients in the study by Schillaci et al. This association was not significant in the bottom and top quartiles of $r^2$. At variance with the report by Schillaci et al, we noticed that the associations of AASI with its major determinants across quartiles of $r^2$ were similar in dippers and nondippers.

Table 3. Adjusted Regression Coefficients of AASI in the Whole Study Population and Across Quartiles of the Goodness-of-Fit of AASI

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects</th>
<th>Low</th>
<th>Medium-Low</th>
<th>Medium-High</th>
<th>High</th>
<th>$P$ vs Low Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>7604</td>
<td>1901</td>
<td>1906</td>
<td>1906</td>
<td>1901</td>
<td></td>
</tr>
<tr>
<td>Partial regression coefficient± SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, +10 y</td>
<td>25.1±1.7†</td>
<td>10.4±3.1‡</td>
<td>9.0±2.4‡</td>
<td>20.7±2.4‡</td>
<td>29.3±2.2‡</td>
<td>0.720</td>
</tr>
<tr>
<td>Body height, +10 cm</td>
<td>−9.4±2.9‡</td>
<td>−8.9±5.3</td>
<td>−5.6±4.0</td>
<td>−15.6±4.1‡</td>
<td>−12.9±3.8‡</td>
<td>0.620</td>
</tr>
<tr>
<td>24-h mean pressure, +10 mm Hg</td>
<td>2.2±2.0</td>
<td>1.5±3.4</td>
<td>0.7±2.8</td>
<td>6.5±2.9†</td>
<td>13.3±2.7‡</td>
<td>0.860</td>
</tr>
<tr>
<td>24-h heart rate, +10 bpm</td>
<td>−12.7±2.1‡</td>
<td>−1.7±3.5‡</td>
<td>−10.6±2.3‡</td>
<td>−8.5±3.0†</td>
<td>−14.3±2.9‡</td>
<td>0.018</td>
</tr>
</tbody>
</table>

All of the regression coefficients were mutually adjusted and, in addition, accounted for cohort and sex. The partial regression coefficients were multiplied by $10^3$ to remove leading zeros.

Significance of the regression coefficients: *$P<0.05$; †$P<0.01$; ‡$P<0.001$.
Li et al measured AASI and aortic pulse wave velocity on the same day in 166 Chinese volunteers. They found a close relation between these indices of arterial stiffness, which was consistent in women \((r=0.58; P<0.0001)\) and men \((r=0.38; P=0.002)\) and in young \((<40 \text{ years}; r=0.26; P=0.02)\) and older adults \((r=0.25; P=0.02)\). AASI was also significantly related to aortic pulse wave velocity in 99 diastolic dippers \((r=0.27; P=0.007)\), as well as in 67 diastolic nondippers \((r=0.41; P=0.0005)\). Schillaci et al also measured both indices on the same day. In 346 untreated hypertensive patients, they reported a direct correlation between AASI and aortic pulse wave velocity of 0.28 \((P<0.001)\). In 1678 subjects randomly recruited from the population of Copenhagen, the correlation coefficient between AASI and aortic pulse wave velocity was only 0.02 \((P=0.47)\). In view of our current results, we computed the correlation coefficients between the 2 indices in the lowest and highest quartiles of the distribution of the goodness-of-fit of the AASI regression line in the Danish cohort. These correlation coefficients were \(-0.007 (P=0.89)\) and 0.22 \((P<0.0001)\), respectively \((P \text{ value for the difference: } <0.0001)\). These unpublished observations, along with the present findings, suggest that a better fit of the AASI regression line in individual subjects might enhance the accuracy of AASI as a measure of arterial stiffness.

The present study has limitations and strengths. First, the 6 populations differed in anthropometric characteristics and lifestyle. However, the correlations of AASI with the determinants of the association between diastolic and systolic blood pressures were adjusted for one another at the level of individual subjects. Sensitivity analyses showed that our findings were consistent in dippers and nondippers, in women and men, in various ethnic groups, and with extensive multivariable adjustments applied. Second, ambulatory blood pressure monitoring was not standardized across the 6 contributing studies in terms of device type and intervals between readings. However, across cohorts, we used the same SAS program to compute blood pressure–derived variables that were time weighted. Sensitivity analyses from which we excluded the auscultatory recordings were also confirmatory. Third, as suggested by experts in the field, AASI is an indirect measure of arterial stiffness and is under the influence of other hemodynamic factors, such as wave reflections originating from peripheral sites, stroke volume, and peripheral resistance. The range of diastolic and systolic blood pressure values, which itself depends on the duration of the awake and asleep periods and on the intensity of physical activity during daytime, might additionally influence AASI. Nevertheless, in collaboration with the Ohasama investigators, we demonstrated recently that random exclusion of readings from ambulatory recordings with measurements programmed at 30-minute intervals did not significantly change the average value of AASI until >7 readings were disregarded. Finally, we chose to use the calculated instead of the measured mean arterial pressure, because in most patients the measured mean arterial pressure was unavailable for analysis. However, the concordance between computed and measured mean arterial pressures was high in 1493 participants with available data.
**Perspectives**
A higher goodness-of-fit of the AASI regression line in individual subjects strengthens the association with its known determinants and likely enhances the statistical power of analyses involving AASI as a marker of arterial stiffness. Our findings have implications for clinical practice and research. The $z$ score for the association of AASI with the 4 determinants of arterial stiffness combined (age, height, mean arterial pressure, and heart rate) increased curvilinearly with $r^2$, with most of the increase occurring above the 20th percentile of $r^2$ (0.36). One might use this threshold in clinical practice as the minimum value of $r^2$, when AASI is applied for the risk stratification of individual patients. On the other hand, in clinical research, it is not good practice to exclude subjects from statistical analyses based on an arbitrary threshold. We would suggest that future reports of research on AASI might include a sensitivity analysis, excluding subjects with the $r^2$ value set at a threshold of 0.36. However, primary analyses should always include all of the subjects, because a low $r^2$ might also reflect disconnection of diastolic from systolic blood pressure because of cardiovascular disease.

**Acknowledgments**
We gratefully acknowledge the secretarial assistance of Sandra Covens and Ya Zhu (Studies Coordinating Centre, University of Leuven, Leuven, Belgium).

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**Disclosures**
None.
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Ahmet Adiyaman, Dirk G. Dechering, José Boggia, Yan Li, Tine W. Hansen, Masahiro Kikuya, Kristina Björklund-Bodegård, Tom Richart, Lutgarde Thijs, Christian Torp-Pedersen, Takayoshi Ohkubo, Eamon Dolan, Yutaka Imai, Edgardo Sandoya, Hans Ibsen, Jiguang Wang, Lars Lind, Eoin O’Brien, Theo Thien, Jan A. Staessen, on behalf of the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) Investigators

Word Counts: manuscript 3351

Number: Tables 4, Figures 2

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Expanded Methods
Study Population
Previous publications described the construction of the IDACO database. After an electronic search of the literature, we included studies if they involved a random population sample. All studies included in the IDACO database received ethical approval and have been reported in peer-reviewed publications. For the current analysis, we considered the baseline data of 2311 residents from Copenhagen, Denmark; 2542 subjects from Noorderkempen, Belgium; 1221 older men from Uppsala, Sweden; 1535 inhabitants from Ohasama, Japan; 360 villagers from the JingNing county, China; and 1859 subjects from Montevideo, Uruguay. All participants gave informed written consent. Of the 9828 subjects, we excluded 2224 participants (22.6%), because they were less than 18 years old at enrolment (n=17), or because their 24-h ambulatory recording included less than 30 readings in total (n=563), or less than 5 nighttime readings (n=1644). The number of participants statistically analyzed amounted to 2138 from Copenhagen; 1127 from Noorderkempen; 1100 from Uppsala; 1520 from Ohasama; 349 from JingNing; and 1370 from Montevideo.

Blood Pressure Measurement
We programmed blood pressure monitors to obtain ambulatory readings at 30-minute intervals throughout the whole day, or at intervals ranging from 155 to 306 minutes during daytime and from 305 to 606 minutes at night. The devices implemented an auscultatory algorithm (Accutracker II, Suntech Medical Instruments Inc., Morrisville, NC) in Uppsala or an oscillometric technique (SpaceLabs 90202 and 90207, SpaceLabs Inc., Redmond, WA) in Noorderkempen, Montevideo and JingNing. The Takeda TM-2421 recorders (A&D, Tokyo, Japan) and the ABPM-630 devices (Nippon Colin, Komaki, Japan), used in Copenhagen and Ohasama, respectively, implemented both techniques, but we only analyzed the oscillometric readings. The Ohasama recordings were edited sparsely according to previously published criteria, but all other recordings remained unedited. We used linear regression, weighted by the time-interval between successive readings, to determine the regression slope of diastolic on systolic pressure in individual recordings. We did not force the regression slope through the origin, because during diastole when blood flow drops to zero, such a phenomenon does not occur for blood pressure. We defined AASI as unity minus the regression slope. Pulse pressure was systolic minus diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure. Because the oscillometrically measured mean arterial pressure was not available in all cohorts, we computed mean arterial pressure as diastolic blood pressure plus one third of pulse pressure. We studied the concordance between the computed and the oscillometrically measured mean arterial pressure in 1144 Belgian and 349 Chinese participants. Ambulatory hypertension was a 24-h blood pressure of 130 mm Hg systolic or 80 mm Hg diastolic, or higher, or the use of antihypertensive drugs.
While accounting for the daily pattern of activities of the participants, we defined daytime as the interval ranging from 10 AM to 8 PM in Europeans and South Americans, and from 8 AM to 6 PM in Asians. The corresponding nighttime intervals ranged from midnight to 6 AM and from 10 PM to 4 AM, respectively. These fixed intervals eliminate the transition periods in the morning and evening when blood pressure changes rapidly, resulting in daytime and night-time blood pressure levels that are within 1–2 mm Hg of the awake and asleep levels. In dichotomous analyses, we defined nondipping as a night-to-day ratio of systolic blood pressure of 0.90 or higher.

Other Measurements
We used the questionnaires originally administered in each cohort to obtain information on each subject’s medical history, and smoking and drinking habits. Body mass index was body weight in kilograms divided by height in meters squared. We measured serum cholesterol and blood glucose by automated enzymatic methods. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 mmol/L (126 mg/dL) or 11.1 mmol/L (200 mg/dL), respectively, or the use of anti-diabetic drugs.

Statistical Analyses
For database management and statistical analyses, we used SAS software, version 9.1.3 (SAS Institute, Cary, NC) and its JMP add-on, version 6.0. We checked that the assumption of normality was applicable to the variables under study by normal probability plots. We compared means and proportions by the large sample z-test and by the $\chi^2$ statistic, respectively. Statistical significance was a two-sided $P$-value of 0.05.

In single and multiple regression analyses, the established determinants of the relation of diastolic on systolic blood pressure were age, body height, 24-h mean arterial pressure, and 24-h heart rate. In single regression analysis, we also considered the night-to-day ratio of systolic blood pressure and 24-h pulse pressure. Multivariable-adjusted models included as covariables cohort and/or sex, as appropriate, and age, body height, 24-h mean arterial pressure, and 24-h heart rate. In sensitivity analyses, we additionally adjusted for serum total cholesterol, smoking, antihypertensive drug treatment, diabetes mellitus and a history of cardiovascular disease.

We subdivided the study population in cohort and sex-specific quartiles of the goodness of fit of the slope of diastolic on systolic blood pressure. We used the coefficient of determination ($r^2$) as a measure of the goodness of fit. We compared Pearson’s correlation coefficients across quartiles, using Fisher’s z-transform. In multivariable-adjusted analyses, we compared the partial regression coefficients across quartiles, using appropriate interaction terms with 3 design variables coding for the quartiles of $r^2$. In the last step of the analyses, we computed a cumulative z-score for the single correlation coefficients of AASI with age, body height, 24-h mean arterial pressure, and 24-h heart rate. For each subject, we then computed a cumulative z-score as the sum of the unsigned $z$-values for the 4 single correlation coefficients of AASI. We plotted the average cumulative z-score against the goodness of fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (approximate 90th percentile of $r^2$) by steps of 0.01.
References


Appendix

IDACO Centers and Investigators

Database Management and Coordination
J Boggia, TW Hansen, M Kikuya, Y Li, JA Staessen (project coordinator), and L Thijs (supervisor database management) constructed the IDACO database at the Studies Coordinating Centre in Leuven, Belgium.
Table S1. Correlates of AASI in the Whole Study Population and in the lowest and highest quartiles of the Goodness of Fit of AASI by Sex and Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Low</th>
<th>High</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n = 3472)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.35‡</td>
<td>0.16‡</td>
<td>0.57‡</td>
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<tr>
<td>Body height</td>
<td>–0.06‡</td>
<td>–0.04</td>
<td>–0.49‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean pressure</td>
<td>0.12‡</td>
<td>0.04</td>
<td>0.24‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h heart rate</td>
<td>–0.18‡</td>
<td>–0.15‡</td>
<td>–0.36‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Men (n = 4132)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.37‡</td>
<td>0.21‡</td>
<td>0.52‡</td>
<td>&lt;0.001</td>
</tr>
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<td>Body height</td>
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<td>–0.02</td>
<td>–0.24‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h mean pressure</td>
<td>0.12‡</td>
<td>0.05</td>
<td>0.14‡</td>
<td>0.003</td>
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<tr>
<td>24-h heart rate</td>
<td>–0.13‡</td>
<td>–0.04</td>
<td>–0.22‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Europeans (n = 4365)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.37‡</td>
<td>0.12‡</td>
<td>0.49‡</td>
<td>&lt;0.001</td>
</tr>
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<td>–0.02</td>
<td>–0.13‡</td>
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<tr>
<td>24-h mean pressure</td>
<td>0.15‡</td>
<td>0.03</td>
<td>0.27‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h heart rate</td>
<td>–0.13‡</td>
<td>–0.02</td>
<td>–0.14‡</td>
<td>0.003</td>
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<tr>
<td><strong>Asians (n = 1869)</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Age</td>
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<td>–0.18‡</td>
<td>–0.22‡</td>
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<tr>
<td>24-h mean pressure</td>
<td>0.05*</td>
<td>0.02</td>
<td>0.21‡</td>
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<td>24-h heart rate</td>
<td>–0.12‡</td>
<td>–0.05</td>
<td>–0.24‡</td>
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</tr>
<tr>
<td><strong>South Americans (n = 1370)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.22‡</td>
<td>0.12*</td>
<td>0.33‡</td>
<td>0.002</td>
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<tr>
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<td>–0.03</td>
<td>–0.09</td>
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<td>0.11‡</td>
<td>0.03</td>
<td>0.21‡</td>
<td>0.009</td>
</tr>
<tr>
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<td>–0.17‡</td>
<td>–0.07</td>
<td>–0.23‡</td>
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</tbody>
</table>

AASI is the ambulatory arterial stiffness index. The P-values are for the differences in the correlation coefficients between the lowest and highest quartiles of the goodness of fit of AASI.

Significance of the correlation coefficients: * P ≤ 0.05; † P < 0.01; ‡ P < 0.001.
Table S2. Adjusted Regression Coefficients in the Whole Study Population and in the Lowest and Highest Quartiles of the Goodness of Fit of AASI by Sex and by Ethnicity

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Low</th>
<th>High</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n = 3472)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>32.1±2.4 ‡</td>
<td>11.4±4.2 †</td>
<td>27.7±3.4 ‡</td>
<td>0.003</td>
</tr>
<tr>
<td>Body height (+10 cm)</td>
<td>–8.9±4.3*</td>
<td>–15.2±7.4 *</td>
<td>–13.8±5.7 *</td>
<td>0.88</td>
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<td>24-h mean pressure (+10 mmHg)</td>
<td>–1.4±2.9</td>
<td>–0.5±4.9</td>
<td>14.1±3.8 ‡</td>
<td>0.019</td>
</tr>
<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>–12.8±3.2 ‡</td>
<td>–8.2±5.5</td>
<td>–16.3±4.4 ‡</td>
<td>0.250</td>
</tr>
<tr>
<td><strong>Men (n = 4132)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>18.4±2.4 ‡</td>
<td>10.9±4.7 *</td>
<td>28.1±3.1 ‡</td>
<td>0.002</td>
</tr>
<tr>
<td>Body height (+10 cm)</td>
<td>–11.1±3.8 †</td>
<td>–3.2±7.4</td>
<td>–13.8±5.2 †</td>
<td>0.24</td>
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<tr>
<td>24-h mean pressure (+10 mmHg)</td>
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<td>–2.1±4.6</td>
<td>11.7±3.9 †</td>
<td>0.022</td>
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<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>–11.5±2.7 ‡</td>
<td>0.1±4.8</td>
<td>–11.3±3.9 †</td>
<td>0.065</td>
</tr>
<tr>
<td><strong>Europeans (n = 4365)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>23.6±2.5 ‡</td>
<td>9.3±4.7 *</td>
<td>26.2±3.4 ‡</td>
<td>&lt;0.001</td>
</tr>
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<td>Body height (+10 cm)</td>
<td>–5.9±3.8</td>
<td>–0.8±6.6</td>
<td>–12.4±5.5 *</td>
<td>0.18</td>
</tr>
<tr>
<td>24-h mean pressure (+10 mmHg)</td>
<td>0.2±2.7</td>
<td>–2.8±4.3</td>
<td>9.7±4.3 *</td>
<td>0.026</td>
</tr>
<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>–12.1±2.7 ‡</td>
<td>–2.7±4.4</td>
<td>–7.6±4.2</td>
<td>0.420</td>
</tr>
<tr>
<td><strong>Asians (n = 1869)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>34.5±2.6 ‡</td>
<td>20.3±5.2 ‡</td>
<td>24.3±3.6 ‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body height (+10 cm)</td>
<td>–7.4±4.5 †</td>
<td>–10.1±9.0</td>
<td>–7.8±5.5</td>
<td>0.82</td>
</tr>
<tr>
<td>24-h mean pressure (+10 mmHg)</td>
<td>4.2±2.8</td>
<td>10.9±4.7 *</td>
<td>14.3±3.7 ‡</td>
<td>0.57</td>
</tr>
<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>–1.6±3.4</td>
<td>–3.0±6.2</td>
<td>–12.7±4.4 †</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>South Americans (n = 1370)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>18.0±3.8 ‡</td>
<td>10.4±6.4</td>
<td>24.8±6.7 ‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body height (+10 cm)</td>
<td>–23.6±7.8 †</td>
<td>–9.9±14.2</td>
<td>–19.2±12.0</td>
<td>0.62</td>
</tr>
<tr>
<td>24-h mean pressure (+10 mmHg)</td>
<td>5.1±5.3</td>
<td>–3.8±8.6</td>
<td>–20.7±9.1 *</td>
<td>0.18</td>
</tr>
<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>–25.7±5.8 ‡</td>
<td>–6.1±9.9</td>
<td>–33.0±9.0 ‡</td>
<td>0.039</td>
</tr>
</tbody>
</table>

AASI is the ambulatory arterial stiffness index. All regression coefficients were mutually adjusted and in addition accounted for cohort (except in South Americans). The associations in different ethnic groups were also adjusted for sex. The partial regression coefficients were multiplied by 10³ to remove leading zeros. The P-values are for the differences in the regression coefficients between the lowest and highest quartiles. Significance of associations: * P≤0.05; † P<0.01; ‡ P<0.001.
Table S3. Correlation Coefficients of AASI in the All Subjects and by Quartiles of the Goodness of Fit of AASI — Sensitivity Analysis Excluding 1100 Auscultatory Recordings

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects</th>
<th>Quartiles of the goodness of fit ($r^2$) of the AASI regression line</th>
<th>P-value versus low group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Medium-low</td>
</tr>
<tr>
<td>Number</td>
<td>6504</td>
<td>1580</td>
<td>1667</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness of fit ($r^2$)</td>
<td>0.73±0.15</td>
<td>0.52±0.12</td>
<td>0.71±0.03</td>
</tr>
<tr>
<td>AASI</td>
<td>0.44±0.17</td>
<td>0.60±0.15</td>
<td>0.45±0.13</td>
</tr>
<tr>
<td>Correlation coefficient of AASI with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.32‡</td>
<td>0.18‡</td>
<td>0.32‡</td>
</tr>
<tr>
<td>Body height</td>
<td>-0.05‡</td>
<td>-0.02</td>
<td>-0.12‡</td>
</tr>
<tr>
<td>24-h mean arterial pressure</td>
<td>0.15‡</td>
<td>0.06*</td>
<td>0.12‡</td>
</tr>
<tr>
<td>24-h heart rate</td>
<td>-0.17‡</td>
<td>-0.13‡</td>
<td>-0.21‡</td>
</tr>
<tr>
<td>24-h pulse pressure</td>
<td>0.47‡</td>
<td>0.32‡</td>
<td>0.42‡</td>
</tr>
<tr>
<td>Systolic nigh-to-day ratio</td>
<td>0.15‡</td>
<td>-0.06</td>
<td>-0.22‡</td>
</tr>
<tr>
<td>Serum total cholesterol</td>
<td>0.11‡</td>
<td>0.09‡</td>
<td>0.08‡</td>
</tr>
</tbody>
</table>

AASI is the ambulatory arterial stiffness index. Significance of the correlation coefficients: * $P \leq 0.05$; † $P<0.01$; ‡ $P<0.001$. 
Table S4  Mutually Adjusted Associations of AASI with Established Determinants of Arterial Stiffness in the Whole Study Population and Across Quartiles of the Goodness of Fit of AASI— Sensitivity analysis excluding 1100 auscultatory recordings

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects</th>
<th>Quartiles of the goodness of fit ($r^2$) of the AASI regression line</th>
<th>P-value versus low group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6504</td>
<td>Low</td>
<td>Medium-low</td>
</tr>
<tr>
<td>Number</td>
<td>1580</td>
<td>1667</td>
<td>1616</td>
</tr>
<tr>
<td>Partial regression coefficient (±SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (+10 years)</td>
<td>28.1±1.7‡</td>
<td>9.9±3.0‡</td>
<td>13.5±2.5‡</td>
</tr>
<tr>
<td>Body height (+10 cm)</td>
<td>-4.3±2.5</td>
<td>-13.1±4.8†</td>
<td>-19.9±3.7</td>
</tr>
<tr>
<td>24-h mean pressure (+10 mmHg)</td>
<td>9.0±2.2‡</td>
<td>3.5±3.6</td>
<td>6.1±3.1*</td>
</tr>
<tr>
<td>24-h heart rate (+10 bpm)</td>
<td>-10.5±2.3‡</td>
<td>-7.0±3.9</td>
<td>-7.5±3.3*</td>
</tr>
</tbody>
</table>

AASI is the ambulatory arterial stiffness index. All regression coefficients were mutually adjusted and were in addition adjusted for cohort and sex. The partial regression coefficients were multiplied by $10^3$ to remove leading zeros. Significance of the associations: * $P \leq 0.05$; † $P < 0.01$; ‡ $P < 0.001$. 
Legends to Figures

**Figure S1.** Scatterplot of the measured on the computed mean arterial pressure (MAP) in 1493 subjects. The slope ($P=0.87$) and the intercept ($P=0.54$) of the regression line (blue; $r=0.98; P<0.0001$) did not differ from the parameters of the line of identity (black). The dotted lines delineate a 5 mm Hg interval above and below the regression line.

**Figure S2.** Plot of the average cumulative z-score against the goodness of fit of the AASI regression line, going from $r^2=0$ to $r^2=0.80$ (approximate 90th percentile of $r^2$) by steps of 0.01. The cumulative z-score is the sum of the unsigned Fisher z-transforms of the single correlations of AASI with age, body height, 24-h mean arterial pressure, and 24-h heart rate. Vertical lines denote percentiles of the distribution of the goodness of fit ($r^2$). This sensitivity analysis excludes 1100 auscultatory recordings.
Figure S1

Measured MAP vs. Computed MAP

\[ y = -0.95 + 1.003x \]
\[ n = 1493 \]
\[ r = 0.98 \ (P<0.0001) \]
Figure S2

Cumulative Z-score vs. Goodness of Fit ($R^2$)
Chapter 5.1

General discussion and summary
General discussion and summary

A large body of evidence supports the notion that cardiovascular disease is for the most preventable by interventions like exercise, modified diets, statins and antihypertensive therapy[1]. Hypertension is an established and well known risk factor both for cerebrovascular and cardiac disease.

Systolic BP increases with age until the eighth or ninth decade of life[2]. In contrast, diastolic BP rises only until middle age and then either levels off or decreases slightly. With increasing age, there is a gradual shift from diastolic BP to systolic BP as main predictor of cardiovascular risk[3]. From 60 years of age onward, coronary heart disease risk is positively correlated with systolic BP but is inversely related to diastolic BP.[4] Reduction of systolic BP is beneficial over the whole range of systolic blood pressures. Reducing diastolic BP is also beneficial, but too much reduction could be harmful (because of reduced perfusion of the coronary arteries)[5]. Whether or not the J-curve phenomenon for diastolic BP is attributable to antihypertensive treatment has been debated over the past decades. In general, one could opt to reduce systolic BP in patients with high cardiovascular risk according to the guidelines (office BP <140/90 or <130/80 in patients with a history of cardiovascular, renal disease or diabetes mellitus)[6]. For diastolic BP, given the results of the above cited literature, one should adopt a prudent approach in patients with concomitant coronary heart disease, in whom diastolic BP should probably not be lowered to less than 70 mm Hg, whereas the lower border could be at least 55 mmHg for others.[5]

The choice of which antihypertensive drugs are started to reduce BP is of minor importance, as a large body of evidence has shown that the BP reduction itself is what matters in term of cardiovascular risk reduction[7, 8]. Effects beyond BP reduction (antihypertensive class effects) account for only 10-15%. The only exception could be monotherapy with beta-blockers. Beta-blockers are nowadays not recommended as monotherapy for hypertension, because of their weak ability to reduce stroke incidence, compared to other antihypertensives, like calcium channel blockers, thiazide diuretics, ace-inhibitors or angiotensin II receptor antagonists[9]. This could be because of their "pseudo-antihypertensive" efficacy (failure to lower central aortic pressure)[10]. Of course, for other indications (such as during or after cardiac ischaemia, in heart failure, certain types of arrhythmia and hypertrophic obstructive cardiomyopathy), monotherapy with a beta-blocker could still be a good choice[9, 11]. Otherwise, combining beta-blockers with vasodilating antihypertensives could be advised.

Blood pressure measurement; the procedure

The biological variability of BP is high[12], and many factors influence BP itself or the BP measurement[13-17]. The procedure of BP measurement in the office should therefore be highly standardized. Some reminders for adequate performance of sitting BP measurement are: Instruct patients not to drink coffee or eat meals hours before the measurement. Let the patient rest for at least 5 minutes, if possible, 10 minutes. Although bare arm is ideal, there is discussion about the fact if BP should not be measured with the cuff placed over clothing. The patient should not talk or perform other activity while BP is measured.

We have shown in this thesis (chapter 2.1) that the arm should be supported at heart level, as the BP could be 0.49 mmHg systolic and 0.47 mmHg diastolic BP higher for every cm of the cuff under the level of the right atrium. In our hands, this represented 9.3/9.4 mmHg overestimation of BP when the arm was placed on a chair support (67.5 cm high), and 6.1/5.7
mmHg overestimation when the arm was placed on the desk (77.0 cm high). A systolic BP difference of these magnitudes represents a 10-15% risk difference in coronary heart disease, 18-27% difference in stroke, 12-18% difference in total cardiovascular mortality, and 6-9% difference in all-cause mortality rates[18]. Use a chair that supports the back. Make sure that the legs are uncrossed and feet flat on the floor. In this thesis (chapter 2.2), we proved that leg crossing at the level of the knees raised the mean BP up to 7.9/2.3 mmHg for systolic/diastolic BP, with higher values especially in hypertensives and diabetics. This systolic BP difference represents an overestimation of cardiovascular risk by approximately 12, 23 and 15% for coronary heart disease, stroke, and total cardiovascular mortality respectively. We additionally proved (chapter 2.3) that a higher stroke volume was the reason of the rise of BP when crossing the legs at the level of the knee. Therefore, both in BP studies and in future guidelines, arm and leg position during BP measurement should explicitly be mentioned.

Blood pressure measurement; progress

Differences in the office versus at home

Home BP has revealed that significant differences can exist between office and home[19]. These differences are largely determined by other factors than the presence of a doctor. It appears that the hospital environment has a more important contribution. In our hands for example (chapter 3.2), approximately 2/3 of the systolic BP differences were caused by the hospital environment and only 1/3 by the entrance of the doctor. Diastolic BP differences were explained for approximately 75% by the hospital environment and for 25% by the entrance of the doctor.

The clinical significance of “white coat” hypertension (WCH), a condition in which BP is slightly elevated in the clinic environment but normal in daily life, is controversial[20-22]. Although in general there seems no substantial higher cardiovascular risk compared to normotensives in trials with relatively short follow-up[23, 24], some studies with longer follow-up have shown a higher cardiovascular risk in WCH compared to normotensives[21, 22, 25]. Masked hypertension (MH), a condition in which BP is normal in the clinic environment but elevated in daily life, has a similar prevalence in the population as WCH (10-20%)[26]. For MH, in which hypertension is hidden from the doctor and therefore not adequately treated, there is consistent evidence in those patients that the cardiovascular risk is higher than in normotensives, and almost as high as in hypertensives[27-29]. This indicates that it is essential to include out of office BP measurement (self measured BP at home or 24-hour ambulatory BP monitoring) in cardiovascular risk stratification.

Self blood pressure measurement

Self measured BP is increasingly being used with the introduction of fully automated and cheap devices[30]. Is has proven to have a better reproducibility than conventional office measurement and it provides more accurate estimates of the daily BP, resulting in higher predictive value for cardiovascular disease[6, 31]. Because of the different environmental setting in which BP is measured and because of the difference in measurement technique (auscultatory versus oscillometric)[32], different cut-offs are present for hypertension. A review of 30 years of research (chapter 3.1 of this thesis), regarding cut-off limits results in the following limits for diagnosis and treatment[33]:

187
### Table 1. Thresholds for optimal, normal and high BP for home BP measurement.

<table>
<thead>
<tr>
<th></th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal home BP</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal home BP</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>High home BP</td>
<td>≥135</td>
<td>≥85</td>
</tr>
</tbody>
</table>

Treatment should probably be started if home BP is equal to or higher than 135/85 mmHg. Currently, there is no proof that therapeutic thresholds for the home BP should be lower in high-risk compared with normal-risk patients. This should be investigated further in the future. A large body of evidence, however, demonstrated that each millimetre of mercury of BP lowering counts in the prevention of cardiovascular complications and that in high-risk patients even small decreases in BP result in large absolute benefit[7].

### Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) helps to make therapeutic decisions in patients who exhibit discordance between clinic and ambulatory BP values (WCH, resistant hypertension and MH)[34]. It has also augmented our understanding of BP circadian rhythm (24-hour period and night-day patterns) and has become an efficacious instrument aiding therapeutic decisions in hypertensive patients and other subjects at risk for cardiovascular disease[35]. ABPM is more strongly correlated with target-organ damage than office BP and offers more accurate prognostic information of cardiovascular outcomes[6, 36].

Each 5% attenuation in the decline in nocturnal systolic/diastolic BP confers approximately a 20% rise in the risk of cardiovascular mortality[37]. Subjects with a less than 10% nighttime BP decrease (non-dippers), or even an increase in BP during the night were those to exhibit a worse cardiovascular prognosis[38]. The dipping phenomenon is however poorly reproducible and should therefore be interpreted carefully[37]. Independent of the nocturnal dipping, high nocturnal BP is an additional determinant of an unfavourable prognosis. Nocturnal BP seems to correlate better with signs of target organ damage and cardiovascular morbidity than daytime BP[36, 39]. Both nondipping and high nighttime BP share common determinants such as sympathetic overactivity, sleep apnoea, pressure-dependent natriuresis and underlying organ damage. It could therefore be that non-dipping and high nighttime BP are a consequence of hypertensive target organ damage and tend to occur when target organ damage is present. Therefore it is hypothesized that these phenomena indicate reverse causality[37]. For diagnostic uses therefore, these parameters are useful, however for treatment purposes, it is debatable if these parameters themselves should be targeted (chronotherapy)[40]. It may be more logical to vigorously treat the underlying disease or risk factors. For thresholds of the measures determined by 24-hour ABPM, we refer to table 2 and to the guidelines[6].

### Table 2. Diagnostic thresholds for conventional and ambulatory hypertension.

<table>
<thead>
<tr>
<th></th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional BP</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>24-h ambulatory BP</td>
<td>125-130</td>
<td>80</td>
</tr>
<tr>
<td>24-h daytime BP</td>
<td>130-135</td>
<td>85</td>
</tr>
<tr>
<td>24-h nighttime BP</td>
<td>120</td>
<td>70</td>
</tr>
</tbody>
</table>
Blood pressure measurement; process

Arterial stiffness processed from ambulatory blood pressure

Ageing and atherosclerosis contribute to stiffening of the arteries. The properties of the walls of large arteries change and eventually result in plaque formation and ischaemic events (heart attack, stroke etc.)[41, 42]. New indexes are increasingly being implemented in cardiovascular risk stratification, beyond the classic Framingham risk score (cholesterol, age, sex, BP, smoking etc). Indexes like intima media thickness (highly standardized measurement of arterial vessel wall thickness by ultrasonography), coronary calcium score (CT indexed evaluation of calcium deposits in the coronary vasculature), and indexes of arterial stiffness, like pulse wave velocity (measurement of blood flow velocity over the large arteries by special equipment) have shown to have additional predictive value beyond the classical risk stratification[42-44]. They are however difficult to measure, because of the need for special devices and highly trained technicians, and therefore they are costly.

The ambulatory arterial stiffness index (AASI) is a novel marker of arterial stiffness that can be easily determined from 24-hour BP monitoring[45]. It predicts cardiovascular events (especially stroke) and mortality, above and beyond the classical cardiovascular risk factors, after additional correction for 24-hour pulse pressure and even pulse wave velocity[46]. Furthermore, it is closely related to other measures of arterial stiffness, like the pulse wave velocity and the aortic augmentation index[45]. It predicts target organ damage, e.g. renal insufficiency, (micro)albuminuria and intima media thickness[47, 48]. In chapter 4.1 of this thesis we have compiled nearly all present literature in a review. The AASI appears to be modestly reproducible (chapter 4.2 of this thesis), however it was better reproducible than other ambulatory indices of cardiovascular risk, like dipping status[49]. When quality criteria were set, the AASI had comparable reproducibility as 24-hour pulse pressure, together with an approximately similar reproducibility as the 24-hour systolic BP or diastolic BP in various hypertensive populations. One of these quality criteria is the goodness of fit ($r^2$) of the AASI regression line, which determines the AASI as explained in Figure 1[50].

Figure 1. Three patients with the same ambulatory arterial stiffness index (0.50), approximately the same number of blood pressure readings (49-56), however a different goodness of fit of the regression line ($r^2$ of 0.23 up to 0.86) determining the ambulatory arterial stiffness index.

The higher the scatter around the fitline, the lower the goodness of fit (left in figure 1, $r^2=0.23$) and conversely, the better the correlation of the scatter with the AASI regression line, the better the goodness of fit (right in figure 1, $r^2=0.86$). We have proven in chapter 4.4 that
the higher the $r^2$, the better AASI was associated with determinants of arterial stiffness. This was especially the case when a cut-off value of $r^2=0.36$ was chosen. After this the association of the AASI with established determinants of arterial stiffness rose exponentially[50]. Therefore, in future analyses of AASI, sensitivity analyses should be made excluding data with a $r^2$ lower than 0.36. The $r^2$ could count as a quality criterion for AASI.

Additionally, the novel AASI index created substantial discussion (chapter 4.3)[51-57]. Some authors were very positive naming AASI one of the gems of the 24-hour ABPM, whereas others criticized it as being an indirect measure of arterial stiffness. Comprehensively, a large body of evidence regarding the AASI exists that it predicts cardiovascular target organ damage, cardiovascular events and mortality. The AASI is reproducible and, with the quality criteria that are set, it is ready for the implementation in clinical practice. One of the manufacturers of 24-hour BP measuring devices (Spacelabs), has already implemented the automatical calculation of the AASI in their devices (personal communication prof.dr. J.A. Staessen). Future challenges are to standardize the measurement of AASI further, and to set reference values for different ethnicities and patient groups.
References


Chapter 5.2

Samenvatting
Samenvatting

Cardiovasculaire ziekten, zoals beroertes, hartinfarcten en hartfalen, zijn grotendeels te voorkomen door adequate interventies, zoals verlaging van een verhoogde bloeddruk, lichaamswegening, dieet en cholesterolverlaging[1]. Daarom dient men een hoge systolische bloeddruk bij patienten met een hoog risico op hart- en vaatziekten te verlagen volgens de richtlijnen (<140/90 mmHg of <130/80 mmHg voor mensen met een verleden van hart- en vaatziekten, nierziekten of diabetes mellitus)[2]. Welk bloeddrukverlagend medicijn wordt gestart, is van ondergeschikt belang. Voordat men echter tot behandeling kan overgaan, dient men een nauwkeurige en betrouwbare bloeddruk te verkrijgen. In dit proefschrift zijn wij verder ingegaan op verschillende aspecten die invloed hebben op de meting. Daarnaast zijn wij ingegaan op nieuwe ontwikkeling in risicovoorspelling door middel van bloeddrukmeting, zoals thuisbloeddrukmeting en 24-uurs ambulatoire bloeddrukmeting.

Bloeddrukmeting: de procedure

Bloeddruk is van nature zeer variabel [3], en vele factoren beinvloeden de bloeddruk zelf, of de meting ervan [4-8]. De bloeddrukmeting in de artsenpraktijk moet daarom zoveel als mogelijk gestandaardiseerd zijn. Dat het belangrijk is dat men de arm op harthoogte dient te houden, hebben wij in dit proefschrift (hoofdstuk 2.1) aangetoond. Het blijkt dat elke centimeter onder hartniveau leidt tot een overschatting van de daadwerkelijke bloeddruk. Er was een gemiddelde overschatting van 9,3/9,4 mmHg systolische en diastolische bloeddruk bij het plaatsen van de arm op een armleuning van een stoel. Er was een gemiddelde overschatting van 6,1/5,7 mmHg toen de arm op een bureau werd geplaatst. Het plaatsen van de arm op bureau respectievelijk op de armleuning van een stoel, iets wat frequent wordt gedaan, overschat het risico op hartziekten met 10-15%, het risico op beroertes met 18-27%, de totale cardiovasculaire sterfte met 12-18% en de totale mortaliteit met 6-9%[9]. Er dient vermeden te worden dat de patient de benen of knieën kruist. In dit proefschrift toonden wij aan (hoofdstuk 2.2) dat het kruisen van de benen ter hoogte van de knieën de bloeddruk gemiddeld tot wel 7,9/2,3 mmHg verhoogt, vooral bij patienten met hypertensie en/of diabetes mellitus. Een systolische bloeddruk van deze orde overschat het risico met 12, 23 en 15% op respectievelijk hartziekten, beroertes en totale cardiovasculaire sterfte. Daarnaast toonden wij aan (hoofdstuk 2.3) dat deze bloeddruktijging werd veroorzaakt door een verhoging van het slagvolume. In toekomstige richtlijnen dient daarom aandacht geschonken te worden aan arm- en beenpositie tijdens bloeddrukmeting. Voor gedetailleerde informatie betreffende een correcte bloeddrukmeting, verwijzen we u naar de richtlijnen[10].

Bloeddrukmeting: progressie

Verschillen tussen de artsenpraktijk en thuis

De thuismeting van bloeddruk heeft ons geleerd dat er significante verschillen van bloeddruk tussen de artsenpraktijk en thuis aanwezig kunnen zijn[11]. Tot nu toe werd aangenomen dat de hogere bloeddruk in het ziekenhuis werd veroorzaakt door de arts. Later bedacht men dat ook de ziekenhuisomgeving zelf invloed zou kunnen hebben op de bloeddruk. Wij hebben voor het eerst de afzonderlijke invloeden van de ziekenhuisomgeving en de arts op de bloeddruk onderzocht (hoofdstuk 3.2). Verschillen van bloeddruk tussen thuis en het ziekenhuis blijken grotendeels verklaard te worden door andere factoren dan de binnenkomst van de arts. Wij toonden aan dat de ziekenhuisomgeving zelf een belangrijke bijdrage aan deze verschillen levert. In ons onderzoek bleek bijvoorbeeld dat de verschillen in systolische
bloeddruk thuis ten opzichte van het ziekenhuis voor 2/3 werden verklaard door de ziekenhuisomgeving en voor 1/3 door binnenkomst van de arts. Voor het diastolisch bloeddruksverschil was dit 75% door de ziekenhuisomgeving en 25% door de binnenkomst van de arts.

**Zelfbloeddrukmeting**

De zelfmeting van bloeddruk thuis wordt steeds vaker gebruikt, nu goedkope volautomatische apparaten op de markt zijn gekomen[12]. De thuismeting blijkt een betere risicoschatting op hart- en vaatziekten te geven dan de conventionele spreekuurmeting. Aangezien de bloeddruk op een andere plaats wordt gemeten dan in de spreekkamer of op de polikliniek, en omdat de techniek van de meting anders is, zijn de referentiewaarden ook anders dan die van de praktijkmeting[13]. In **hoofdstuk 3.1** analyseerden wij de aanwezige literatuur van de laatste 30 jaar om afkappunten te formuleren voor optimale, normale en te hoge bloeddruk. Tabel 1 toont de waarden die uit onze analyse kwam[14]:

**Tabel 1.** Afkappunten voor optimale, normale en hoge bloeddruk voor de zelfmeting van bloeddruk thuis.

<table>
<thead>
<tr>
<th></th>
<th>Systolisch (mmHg)</th>
<th>Diastolisch (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimale thuisbloeddruk</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normale thuisbloeddruk</td>
<td>&lt;130</td>
<td>&lt;85</td>
</tr>
<tr>
<td>Hypertensie</td>
<td>≥135</td>
<td>≥85</td>
</tr>
</tbody>
</table>

Dit betekent dat behandeling van de bloeddruk met medicatie dus gestart zou moeten worden als de thuisbloeddruk gelijk of hoger is dan 135/85 mmHg.

**Bloeddrukmeting; processie**

**Arteriestijfheid en 24-uurs ambulatoire bloeddrukmeting**

Ambulatoire bloeddruk monitoring (ABPM) helpt om therapeutische beslissingen te nemen bij personen wiens bloeddruk thuis en in het ziekenhuis verschillend is (witte jas hypertensie en gemaskeerde hypertensie)[15]. Ambulatoire bloeddrukmeting geeft een betere schatting van de kans op cardiovasculaire complicaties dan de conventioneel gemeten bloeddruk[2, 16]. De afkappunten voor de verschillende 24-uurs bloeddrukken zijn samengevat in de onderstaande tabel[2].

**Tabel 2.** Diagnostische afkappunten voor conventionele en ambulatoire hypertensie.

<table>
<thead>
<tr>
<th></th>
<th>Systolisch (mmHg)</th>
<th>Diastolisch (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventionele bloeddruk</td>
<td>140</td>
<td>90</td>
</tr>
<tr>
<td>24-uurs ambulatoire bloeddruk</td>
<td>125-130</td>
<td>80</td>
</tr>
<tr>
<td>24-uurs dagbloeddruk</td>
<td>130-135</td>
<td>85</td>
</tr>
<tr>
<td>24-uurs nachtelijke bloeddruk</td>
<td>120</td>
<td>70</td>
</tr>
</tbody>
</table>

Veroudering en atherosclerose dragen bij aan het stijver worden van de vaten. De samenstelling en functie van de wanden van de slagaders veranderen en uiteindelijk onstaan er vernauwingen in de vaten, die voor beroertes en harteninfarcten kunnen zorgen[17, 18]. De ambulatory arterial stiffness index (AASI) is een nieuwe methode om arteriestijfheid te meten.
en kan makkelijk worden bepaald uit een simpele 24-uurs bloed-drukmeting[19]. In hoofdstuk 4.1 hebben wij samengevat hoe men deze index bepaalt, wat de achterliggende fysiologische mechanismen zijn en welke literatuur er over aanwezig is. De AASI heeft in prospectieve studies bewezen dat het cardiovasculaire aandoeningen (met name beroertes) voorspelt, bovenop de klassieke risicoclassificatie, 24-uurs polsdruk en zelfs pulse wave velocity (de gouden standaard van de bepaling van arteriestijfheid)[20]. Er is aangetoond dat de AASI nauw gelinkerd is aan andere methoden om arteriestijfheid te meten, zoals pulse wave velocity en de augmentatie index[19]. AASI voorspelt hypertensieve eindorgaanschade, zoals nierinsufficiëntie, eiwitverlies in de urine en intima media dikte[21, 22]. Daarnaast hebben wij in hoofdstuk 4.2 onderzocht hoe de reproduceerbaarheid is van deze nieuwe index. De AASI is bescheiden reproduceerbaar gebleken, maar was beter reproduceerbaar dan andere ambulatoire waarden die cardiovasculair risico voorspellen, zoals de mate van nachtelijke bloed-drukdaling[23]. Als kwaliteitscriteria worden gesteld, heeft AASI een vergelijkbare reproduceerbaarheid als 24-uurs polsdruk, niet veel slechter dan 24-uurs systolische en diastolische bloed-druk. Deze nieuwe AASI heeft veel discussie losgemaakt[24-30]. Sommigen waren erg positief en noemden de AASI een van de verborgen schatten van 24-uurs ABPM. Anderen bekritiseerden het, aangezien zijn van mening zijn dat het een indirecte maat is voor arteriestijfheid. In hoofdstuk 4.3 hebben wij enkele discussiepunten over de AASI weergegeven die wij zelf hebben ingebracht. In hoofdstuk 4.4 hebben wij in een grote multi-etnische populatie de betekenis van de “goodness of fit (r²)” verder onderzocht. Hoe meer verspreiding van punten om de regressielijn, zoals links in de figuur, hoe lager de “goodness of fit” en vice versa, zoals rechts in figuur 1 is te zien. We hebben bewezen dat een hogere r² ervoor zorgde dat AASI beter was gelinkerd aan determinanten van arteriestijfheid. Dit was vooral het geval bij een r² hoger dan 0.36, waarna de relatie van AASI met determinanten van arteriestijfheid curvilineair toenam[31]. De hoogte van de r² kan daarom dienen als kwaliteitscriterium voor de meting van de AASI.

Figuur 3. Drie patiënten met dezelfde ambulatoire arteriële stijfheids-index (0.50), ongeveer dezelfde aantal bloed-drukmetingen (49-56), maar een verschillende ‘goodness of fit’ van de regressielijn (r² van 0.23 t/m 0.86) die de ambulatoire arteriële stijfheids-index bepaalt.

Samenvattend is over de AASI in korte tijd al een grote hoeveelheid aan bewijs gevonden dat het verschillende soorten hypertensieve orgaanschade, cardiovasculaire aandoeningen en mortaliteit voorspelt. Het wachten is dan ook op de invoering op grote schaal in de klinische praktijk. Een van de producten van 24-uurs bloed-drukmeters, namelijk Spacelabs, heeft de AASI berekening al geïmplementeerd in hun apparaten (persoonlijke mededeling van prof. dr. J.A. Staessen).
Referenties


Chapter 5.3

Dankwoord
Dankwoord

Het tot stand komen van dit proefschrift is een intensieve doch vruchtbare en leerzame periode geweest. Graag wil ik iedereen danken die direct of indirect heeft bijgedragen aan deze dissertatie. Mijns inziens zijn er belangrijke, wellicht essentiele bijdragen geweest van enkelen.

In het bijzonder wil ik noemen:

Prof. dr. Theo Thien. Mijn primaire promotor en inspiratiebron. Als hoogleraar interne geneeskunde, ervaren clinicus en iemand met een grote wetenschappelijke productie, keek ik tegen u op. U heeft mij al bij het behalen van mijn doctoraal examen toevertrouwd dat ik u Theo mocht noemen. Aangezien ik hier nogal wat moeite mee had, mocht ik van u nog oefenen tot het behalen van mijn artsexamen. Nu na het behalen van mijn artsexamen is het mij nog steeds niet gelukt, echter nu ik op het punt sta om te promoveren, denk ik dat voor mij het moment gekomen is om je Theo te noemen. Theo, ik zal niet vergeten dat je mij in een moeilijke studieperiode, waarin gemakzucht de overhand dreigde te krijgen, bij de hand hebt genomen en uit de misere hebt gesleept. Hiervoor ben ik je erg dankbaar. Daarvoor in de plaats kwam een leergierige, hardwerkende en onderzoeksgerichte student en nu arts. Ik realiseer me dat ik je regelmatig in de avonduren heb “lastiggevallen” en excuseer mij tegenover Saapke, jouw begripvolle partner. Het wekt ongeloof bij andere promovendi als ze horen dat jullie me zelfs in mijn onderzoeksperiode in Leuven hebben opgezocht om te zien hoe het me daar verging. Theo, hartelijk dank voor de talloze uren die je in mij hebt geïnvesteerd, het is een eer om jouw student te zijn geweest.

Prof. dr. Jan Staessen. Mijn tweede promotor en wetenschappelijk wonder. Jan, ik heb bij u een intensieve research fellowship mogen genieten. Het was een ervaring voor mij om te mogen samenwerken met de persoon wiens artikelen ik regelmatig in topbladen als the Lancet en JAMA las. Ook al vinden enkelen op mijn huidige werkplek mij een perfectionist, ik denk dat zij u niet als referentie kennen. De avonden waarin ik met u heb gewerkt, maakten mij al snel duidelijk dat daar wetenschap gebezigd werd op mondiaal topniveau. U bent erg druk met uw bezigheden als hoofd van het Studies Coordinating Centre. Ook al is het moeilijk om uw tempo en werktijden (11.00-01.00, maar eigenlijk 7 dagen, 24 uur per dag) bij te houden, het resultaat is van hoge kwaliteit en kwantiteit. Daarnaast heb ik u leren kennen als een warm, sociaal persoon, die op laagdrempelig niveau omging met zijn studenten. Ik heb begrepen dat dit voor Belgische begrippen uitzonderlijk is. Dank voor alles, en ik hoop dat we in de toekomst kunnen blijven samenwerken.


De leden van de manuscriptcommissie, prof.dr. P. Smits, prof.dr. F. Verheugt en prof.dr. M. Hopman wil ik danken voor het kritisch evalueren van de dissertatie.

Mijn ouders Mehmet en Hatice. Dankzij jullie onvoorwaardelijke steun en opvoeding heb ik zorgeloos en succesvol kunnen studeren. Iets wat jullie, ondanks een hoge intelligentie, door omstandigheden, zelf niet hebben kunnen doen. Jullie emotionele en financiële steun was essentieel voor mijn onderzoeksperiode in het buitenland. Ik hoop dat jullie daarom extra trots
zijn op het feit dat al jullie (drie) kinderen een universitaire studie hebben genoten. Ik dank jullie hierbij ten zeerste voor alles, hoewel ik weet dat ik jullie nooit genoeg kan bedanken.

Mijn broer, drs. Ismail Adiyaman. Bedankt voor de morele steun die je me gedurende mijn onderzoeksperiode hebt gegeven en voor je hulp bij het klaarmaken van het manuscript. Elke keer dat ik het een tijdje niet over de promotie had, bracht jij het weer ter sprake. De snelheid waarmee ik sms’jes van je kreeg als er opnieuw een ‘hit’ van mij op PubMed verscheen, deden mij vermoeden dat je bij PubMed werkt. Echter waarschijnlijk hebben apothekers gewoon lange pauzes en snelle internetverbindingen.

Dr. D.G. Dechering. Dirk, met jou samen ben ik mijn co-schappen begonnen. Samen hebben we nu al meer dan tien publicaties geproduceerd. Je hebt een identiek pad gevolgd van Nijmegen tot Leuven, uiteindelijk resulterend in de specialisatie tot cardioloog. Dank voor je hulp en voor de leuke momenten, zowel op wetenschappelijk als sociaal vlak. Succes met je carrière in Münster.

Alle mede-onderzoekers die actief hebben bijgedragen aan de analyse en verwerking van de data, te weten: Dr. Jose (Pepe) Boggia (internist in Uruguay, mijn onderzoeksmaatje in Leuven), Dr. Lutgarde Thijs (statistisch fenomeen en onderzoeker in Leuven), Dr. Tom Richart (onderzoeker in Leuven), Dr. T. Kuznetsova (onderzoeker in Leuven), Dr. T.W. Hansen (onderzoeker in Denemarken). Uit Nijmegen: drs. Ismail Aksoy, drs. Nevin Tosun en drs. Rutger Verhoeff voor het verzamelen van data die ik heb bewerkt.

Mijn (voor)opleider interne geneeskunde in het Rijnstate Ziekenhuis te Arnhem, Dr. Vera Mattijssen, voor het continu bieden van tijd, ruimte en steun om mijn wetenschappelijke werk en promotie af te maken.

Mijn (voor)opleider cardiologie in het Rijnstate Ziekenhuis te Arnhem, Dr. Hans Bosker, voor de oprechte interesse en de steun die hij mij gaf bij de vorderingen van mijn wetenschappelijke werk en carrièremogelijkheden binnen de cardiologie.


En tenslotte, alle proefpersonen, patienten en vrijwilligers die voor aanvoer van data hebben gezorgd. Zonder jullie kon dit alles niet plaatsvinden! Mijn hartelijke dank.
Chapter 5.4

Curriculum Vitae
Curriculum Vitae


Reeds voor het begin van zijn co-schappen in 2005, begon hij na zijn wetenschappelijke stage, onder leiding van Prof. dr. Th. Thien aan verschillende onderzoeken die nu een onderdeel zijn van het huidige proefschrift (UMC St. Radboud te Nijmegen, Algemene Interne Geneeskunde, Hypertensie en Vasculaire Pathologie). Gedurende de co-schappen werden in de vrije momenten en vakanties belangrijke vorderingen in het onderzoek gemaakt.

Het artsexamen werd behaald in 2007. Reeds voor het artsexamen is hij, gesteund door een Dr. E. Dekker beurs van de Nederlandse Hartstichting, een periode van 4 intensieve maanden research fellow geweest bij Prof. dr. J.A. Staessen aan het Studies Coordinating Centre, Division of Hypertension and Cardiovascular Research aan de Universiteit van Leuven in Belgie. Hier is ook de basis gelegd voor een samenwerkingsverband tussen de Radboud Universiteit (Prof. dr. Th. Thien) en de Universiteit van Leuven (Prof. dr. J.A. Staessen), die tot op heden nog zijn vruchten afwerpt. Thans is de promovendus reviewer voor de vakbladen Hypertension (American Heart Association) en voor the Anatolian Journal of Cardiology (Turkish Heart Association).

Eind 2007 is de promovendus een viertal maanden arts-assistent geweest op de afdeling Hart- en Vaatziekten in het Rijnstate Ziekenhuis in Arnhem (Dr. H.A. Bosker). Direct aansluitend is hij in 2008 in dezelfde kliniek aan zijn vooropleiding Interne Geneeskunde (Dr. L. Verschoor) begonnen, in het kader van zijn opleiding tot cardioloog aan het UMC St. Radboud te Nijmegen. Het plan is om een B-opleidings jaar cardiologie te volgen in het Rijnstate Ziekenhuis te Arnhem (Dr. H.A. Bosker) en aansluitend A-opleiding cardiologie in het UMC St. Radboud te Nijmegen (Prof. Dr. F.W.A. Verheugt en Prof. Dr. J. Smeets). Deze zal in 2013 worden afgerond.
Chapter 5.5

List of publications
List of publications


