

**Nurse Versus Ambulatory Blood Pressure Measurement
in a Community of African Descent: Prevalence and
Significance of “White Coat” Responses**

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Abstract

Hypertension is a major cause of morbidity and mortality in communities of African ancestry. The most appropriate method of predicting the risk for blood pressure (BP)-related cardiovascular events is through 24-hour ambulatory BP (ABP) monitoring. Although the cost of monitors precludes the use of 24-hour BP measurement in groups of African descent in Africa, the extent to which BP-related cardiovascular risk may be underestimated by nurse-derived clinic BP measurements, and the current method of BP-related risk assessment in these communities, is uncertain. In this regard, nurse-derived BP measurement is thought to be superior to other forms of in-office BP measurement.

Ambulatory 24-hour, day and night BP (SpaceLabs, model 90207) and nurse-derived clinic BP (CBP) (mean of 5 values) control rates were determined in 689 randomly selected participants (>16 years) of African ancestry in South Africa. Of the participants 45.7% were hypertensive and 22.6% were receiving antihypertensive medication. More participants had uncontrolled BP at night (34.0%) than during the day (22.6%, $p<0.0001$). However, uncontrolled CBP was noted in 37.2% of participants, while a much lower proportion had uncontrolled ABP (24.1%)($p<0.0001$). These differences were accounted for by a high prevalence of isolated increases in CBP (white-coat effects)(39.4%). Thus, in communities of African descent, despite a worse BP control at night than during the day, a high prevalence of white-coat effects translates into a striking underestimation of BP control when employing CBP rather than ABP measurements.

Nurse-derived BP measurements are often as closely associated with organ damage as ABP. However, the extent to which relationships between nurse-derived BP measurements and organ damage reflect a white-coat effect (isolated increase in in-office BP) as opposed to the adverse effects of BP *per se* are unknown. In 750

participants from a community sample, target organ changes were determined from carotid-femoral pulse wave velocity (PWV) (applanation tonometry and SphygmoCor software) (n=662) and left ventricular mass indexed to height^{2.7} (LVMI) (echocardiography)(n=463). Nurse-derived CBP was associated with organ changes independent of 24-hour BP (LVMI; partial $r=0.15$, $p<0.005$, PWV; partial $r=0.21$, $p<0.0001$) and day BP. However, in both unadjusted ($p<0.0001$ for both) and multivariate adjusted models (including adjustments for 24-hour BP)(LVMI; partial $r=0.14$, $p<0.01$, PWV; partial $r=0.21$, $p<0.0001$) nurse office-day SBP (an index of isolated increases in in-office BP) was associated with target organ changes independent of ambulatory BP and additional confounders. Thus, nurse-elicited white-coat effects account for a significant proportion of the relationship between nurse-derived CBP and target organ changes independent of ambulatory BP. Therefore, high quality nurse-derived BP measurements do not approximate the impact of BP effects *per se* on cardiovascular damage.

In 750 participants from a community sample I evaluated whether nurse office-day BP is inversely related to day-night BP (BP dipping) and whether this relationship may in-part explain the independent association between office-day BP and organ damage. Nurse office-day systolic BP (SBP) was correlated with % night/day SBP ($r=0.22$, $p<0.0001$) and night SBP ($r=0.14$, $p=0.0001$). Although unadjusted and multivariate adjusted (including for day SBP) nurse office-day SBP was associated with LVMI (partial $r=0.15$, $p<0.01$) and PWV (partial $r=0.22$, $p<0.0001$), neither day-night SBP (LVMI; partial $r=-0.01$, $p=0.88$, PWV: partial $r=-0.04$, $p=0.30$) nor % night/day SBP (LVMI; partial $r=0.01$, $p=0.91$, PWV: partial $r=0.04$, $p=0.37$) were independently related to target organ changes. Moreover, the relationships between nurse office-day SBP and target organ changes persisted with adjustments for either day-night SBP ($p<0.05$ - $p<0.0001$) or night SBP ($p<0.01$ - $p=0.0001$). Thus, although nurse office-day SBP, an

index of an alerting response, is independently associated with an attenuation of nocturnal decreases in SBP, neither a decreased BP dipping, nor nocturnal BP explain the independent relationship between nurse office-day SBP and target organ changes.

Whether nurse office-day BP is affected by antihypertensive therapy, is uncertain. In the present study the effect of antihypertensive therapy on nurse office-day BP was assessed in 173 patients whom, off treatment, had a daytime diastolic BP ranging from 90 to 114 mm Hg. Over the treatment period marked decreases in BP occurred ($p < 0.0001$). However, neither nurse office-day systolic (baseline= 16.5 ± 15.8 mm Hg, 4 months= 15.3 ± 18.9 mm Hg, $p = 0.49$), nor diastolic (baseline= 0.9 ± 9.3 mm Hg, 4 months= 4.3 ± 10.7 mm Hg, $p < 0.005$) BP decreased significantly from baseline. Thus, despite producing marked decreases in nurse-derived in-office and out-of-office ambulatory BP, antihypertensive therapy produces no change in nurse-elicited isolated increases in in-office BP (white coat-effects) in a group of African descent.

In conclusion, the results of the present thesis indicate that in an urban, developing community of African descent, as compared to 24-hour BP measurements, nurse-derived BP measurements elicit a significant in-office increase in BP which translates into a marked underestimation of BP control at a community level; is strongly associated with organ damage through effects that cannot be attributed to 24-hour BP or to relationships with an attenuated decline in nocturnal BP; and which cannot be treated with antihypertensive therapy. Further work is required to assess the most cost-effective approach to excluding nurse-elicited isolated increases in in-office BP before initiating antihypertensive therapy to groups of African descent.

DECLARATION

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. The work in this thesis has not been submitted for any degree or examination in this University or any other University.

Joseph Muzi Maseko.....on
this.....day of.....2013

I certify that the studies contained in this thesis have the approval of the Committee for Research in Human Participants of the University of the Witwatersrand, Johannesburg. The ethics approval number is

Joseph Muzi Maseko.....on
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DEDICATIONS

This thesis is dedicated to my wife Nkele Mokgadi Maseko for being my shoulder to lean on and giving me support and encouragement during the writing of this thesis and my three children Thembi, Zintle and Sibusiso who are my inspiration.

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STATEMENT OF MY CONTRIBUTION TO DATA COLLECTION AND ANALYSIS

The studies described in this thesis were designed by myself in consultation with my supervisors. I collected all the clinical data with the assistance of technical staff and my supervisors. As the project coordinator of the study I was also responsible for coordinating the day-to-day running of the study including creating links with the communities where participants were recruited. I performed all the data analysis for this thesis and interpreted these data.

LIST OF ABBREVIATIONS

ABP	Ambulatory Blood Pressure
BMI	Body Mass Index
BP	Blood pressure
CBP	Conventional Blood Pressure
CI	Confidence Intervals
CV	Cardiovascular
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DBPconv	Conventional Diastolic Blood Pressure
DM	Diabetes Mellitus
ECG	Electrocardiogram
ESH	European Society of Hypertension
HbA _{1c}	Glycated Haemoglobin
HDL	High Density Lipoprotein
HT	Hypertensive
HRV	Heart Rate Variability
IVS	Interventricular Septal
LDL	Low Density Lipoprotein
LV	Left Ventricular
LVEDD	Left Ventricular End Diastolic Diameter
LVH	Left Ventricular Height
LVM	Left Ventricular Mass
LVMi	Left Ventricular Mass Index

MAP	Mean Arterial Pressure
NCEP	National Cholesterol Education Program
NT	Normotensive
NICE	National Institute for Health and Clinical Excellence
PR	Pulse Rate
PWT	Posterior Wall Thickness
PWV	Pulse Wave Velocity
SBP	Systolic Blood Pressure
SBPconv	Conventional Systolic Blood Pressure
SD	Standard Deviation
SOWETO	South West Township
WC	Waist Circumference
WHO	World Health Organization

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PREFACE

Hypertension is a major risk factor for cardiovascular disease in both developed and developing countries. A number of studies have shown that twenty four-hour ambulatory blood pressure is more closely associated with target organ changes than conventional blood pressure and therefore it is seen as more appropriate in the diagnosis and management of hypertension. However in spite of all its advantages, the use of ambulatory blood pressure monitoring in a resource limited country like South Africa is almost impossible because it is too expensive. Due to financial constraints, blood pressure monitoring in groups of African descent in Africa is limited to nurse-derived clinic BP measurements. Though nurse-derived is superior to other forms of in-office BP measurement, the extent to which it underestimates BP related cardiovascular risk is uncertain.

In this thesis I therefore explained the extent to which nurse derived BP monitoring underestimates BP control in communities of African descent and whether the main cause of this underestimation is due to the high prevalence of isolated increases in CBP (white-coat effects). Having demonstrated a high prevalence of white coat effects in this community as elicited from nurse derived blood pressure measurement, I subsequently evaluated whether the relationship between nurse derived blood pressure measurement and target organ changes can in-part be attributed to white coat effects. I also noted a strong relationship between white coat effects and target organ changes independent of ambulatory blood pressure. I further evaluated whether this could be attributed to an attenuated decrease in nocturnal blood pressure which frequently occurs in groups of African ancestry and whether white coat effects can be treated with antihypertensive therapy.

This thesis is divided into a number of semi-independent chapters, each with sections that include introduction, methods, results and discussion. The first chapter highlights the current knowledge, understanding and controversies on the role of ambulatory versus office blood pressure, leading to arguments and knowledge gaps that prompted me to perform studies conducted in this thesis. The various chapters in the thesis culminate in a summary chapter which summarises the novel findings and consolidates the different findings of each of the individual chapters. Some of the data in this thesis (Chapters 2 and 3) have been peer reviewed and either published in the *American Journal of Hypertension* (Maseko *et al* 2011) or have received favourable review by the *Journal of Hypertension*. Although the data in Chapters 4 and 5 have not as yet been peer reviewed, these chapters are currently in preparation for submission to reputable international journals.

CHAPTER 1

Superiority of Ambulatory Versus in-Office Blood Pressure Measurement: Current Evidence and Unresolved Issues.

1.1 Introduction

Data obtained from economically developed countries provides convincing evidence that a continuous relationship exists between blood pressure (BP) and the risk of mortality from ischaemic heart disease and stroke (Lewington et al 2002) and hypertension is the second most common risk factor for end stage renal disease (Chobanian et al 2003). In these countries the risk for cardiovascular disease exists in both elderly and in young (18-39 year old) hypertensives (Miura et al 2001). Globally, hypertension contributes to 62% of cerebrovascular disease including strokes, and to 49% of coronary heart disease (WHO 2003). In economically emerging countries such as South Africa, hypertension has materialised as the most prevalent risk factor for heart failure (Stewart et al 2008), coronary artery disease (Steyn et al 2005), and stroke (Mensah 2008, Connor et al 2009).

Hypertension currently affects 1 billion individuals globally and is becoming more prevalent in both economically developed and developing countries (World Health Organisation [WHO] 2003). Estimates of the prevalence of hypertension range from 28% in North America to 44% in some European countries (Wolf-Maier et al 2003). In South Africa, an economically developing country, hypertension affects approximately 26% of the entire population (Steyn et al 2008) but in urbanized populations of African descent living in South Africa, the prevalence may lie between 40 and 50% (Malhotra et al 2008, Maseko et al 2010).

In contrast to the ~34-35% of all hypertensives and 55% of treated hypertensives that are controlled to target BP levels in economically developed countries (Hertz et al 2005, Cutler et al 2008, Wang et al 2007, Wolf-Maier et al 2004), by comparison, data obtained at approximately similar time periods, in an economically emerging country, South Africa, only 14% of all hypertensives (Steyn et al 2001) and 33-44% of treated

hypertensives in primary care settings (Steyn et al 2008, Dennison et al 2007) were controlled to target BP. There is therefore no question that the appropriate detection and management of hypertension is of critical importance in both economically developed and developing (such as South Africa) countries. In this regard, the topic of the most suitable approach to the detection of elevated BP values has been one of ongoing refinement for a number of years, with the most recent debates focussing on whether in-office should be complemented by out-of-office BP measurement.

Despite the well recognised value of in-office BP measurements as cited by all guidelines (WHO 2003, Chobanian et al 2003, Williams et al 2004, Mancia et al 2007, Mendis et al 2007, Flack et al 2010, Seedat and Rayner 2012), there is considerable evidence to show that out-of-office ambulatory BP, where BP is measured using an automated device usually every 15-30 minutes for a 24-hour period, or less frequently at night, offers prognostic information beyond that of in-office BP values (see section 3.0 for a summary of the evidence). This evidence has prompted the British National Institute for Health and Clinical Excellence (NICE) hypertension guidelines committee to recommend the use of ambulatory BP measurements to confirm the presence of hypertension before antihypertensive therapy is initiated (National Clinical Guideline Centre 2011). In-part, this decision was based on cost-effective analyses recently published (Lovibond et al 2011). The ability of ambulatory BP measurements to predict outcomes beyond in-office BP measurements has considerable implications for economically emerging countries, where the likelihood of developing the infrastructure to perform these measurements in the near or even distant future is low. In this regard, the validated devices required to conduct these measurements are just too costly. The question therefore arises as to whether in developing countries, an alternative approach to BP measurement exists which may closely reflect that which can be acquired using ambulatory BP? In this regard, in South Africa, at a primary healthcare level, nurses

manage hypertension and nurses are responsible for BP measurement on the majority of South Africans. In this context the important question is therefore, in South Africa, to what extent do nurse-acquired BP measurements provide different information regarding cardiovascular risk as compared to ambulatory BP?

In the present thesis in an urban, developing community of African ancestry I evaluated the possible public health consequences of performing nurse-acquired in-office BP measurements only. In this regard, I assessed the extent to which aspects of out-of-office ambulatory BP control compare with BP control determined from nurse-acquired in-office BP measurement alone. I also evaluated whether in-office BP measurement utilising carefully obtained nurse-derived BP measurement may be a potentially useful approach to acquiring BP values that are comparative to ambulatory out-of-office BP measurements in predicting target organ changes. Hence, in the present chapter I will summarise the arguments in favour of using out-of-office rather than in-office BP measurement. I will underscore the strengths and weaknesses of the data in favour of using out-of-office ambulatory to complement in-office BP measurement. I will subsequently summarise the evidence that favours nurse-derived BP measurement to provide a better index of cardiovascular risk than that obtained by physicians. In the process of summarising the evidence in favour of out-of-office ambulatory as compared to in-office BP measurement I will underscore the importance of a number of hypotheses developed and tested in the present thesis related to the comparative value of nurse-derived versus ambulatory BP measurement.

1.2 Hypotheses that favour ambulatory out-of-office rather than in-office BP measurements for detecting the risk related to hypertension

A number of hypotheses have been proposed to support the premise that out-of-office ambulatory BP measurements may be better at predicting the cardiovascular risk related to hypertension than in-office BP measurements. In the present section I will describe and explain these hypotheses, and in section 1.3 I will discuss the evidence to either support or refute these hypotheses. I will subsequently highlight the evidence that has not as yet been provided to either support or refute the existing hypotheses and consequently I will underscore the reasons why this missing evidence prompted me to develop additional hypotheses which I tested as part of the present thesis. Why would ambulatory out-of-office BP measurements provide a more accurate risk assessment than in-office BP?

1.2.1 Blood pressure fluctuations over the course of a 24-hour period.

At the most fundamental level, the strongest argument in favour of measuring ambulatory out-of-office rather than in-office BP, is that in-office BP measurement represents a “snapshot” of BP recorded at a single point in time during the course of a day, whereas it is well recognised that marked fluctuations in ambulatory BP may occur over a 24-hour period. Because activity is reduced at night, night BP values decrease considerably as compared to day BP, a change referred to as “BP dipping” (O’Brien et al 1988). Activity levels may represent the strongest determinant of BP during the course of a day or night (Cavelaars et al 2004). An increased nocturnal activity in-part accounts for higher nocturnal BP values than normal (Agarwal et al 2009). In addition however, during the night sympathetic nervous system activity decreases, whilst parasympathetic activity increases (Dodt et al 1997, Sayk et al 2007, Sherwood et al 2002, Nakano et al 2001, Ragot et al 1999, Abate et al 1997), changes that may also contribute toward “BP dipping”. Increases in night BP as compared to normal may occur with a lack of

decrease in nocturnal sympathetic activation (Sayk et al 2007, Sherwood et al 2002, Nakano et al 2001), disturbed baroreflex sensitivity (Vaile et al 1996), sleep apnoea (Young et al 2002), salt sensitivity, where a higher BP at night promotes a pressure natriuresis (Staessen et al 1993, Sachdeva et al 2006) and with changes in nocturnal sleep architecture (Pedulla et al 1995). Clearly, then, a resting in-office BP measurement is likely to be a crude reflection of 24-hour BP values and hence is unlikely to closely represent the pressure load faced by the cardiovascular system.

The hypothesis that out-of-office ambulatory BP provides a better reflection of the daily BP load on the cardiovascular system has been further developed over the years. In this regard, it has been suggested that because day BP incorporates activity levels which are not necessarily constant from day-to-day, that night BP and the lack of extent to which BP decreases at night may be a better reflection of average load on the cardiovascular system (Pickering and Kario 2001). Furthermore, this hypothesis has also been extended to incorporate the consideration that some individuals may have an elevated BP at night, whilst day BP values may be normal and that this entity, called “isolated nocturnal hypertension” may carry a risk for cardiovascular events (Fan et al 2010). The evidence to either support or refute these hypotheses will be provided in the course of the present chapter in section 1.3. Over the years a number of alternative hypotheses that may favour out-of-office ambulatory rather than in-office BP measurements have also been identified. What are these hypotheses?

1.2.2 Isolated in-office or “white-coat” BP effects

In-office BP measurements are well recognised as being on-average higher than not only out-of-office 24-hour BP, which can be accounted for by decreases in BP at night, but also out-of-office day BP values, despite the fact that in-office BP

measurements are obtained at rest, whilst day BP measurements in-part reflect normal daily activities (Floras et al 1981, Mancia et al 1983, Parati et al 1987). This difference has been attributed to artificial increases in BP which occur in the office environment as a consequence of an alerting response, a change often referred to as the “white-coat” effect, a term which attributes this change to the presence of a physician (Mancia et al 1983, Mancia et al 1987, Parati et al 1987, Pickering et al 1988). Over a number of years there has been considerable interest expressed in those individuals with a normal day BP whose in-office BP is nevertheless elevated, and these individuals are often called “white-coat hypertensives”. This is in contrast to those whose in-office BP values are considerably higher than day BP values, but whom nevertheless still have either normotensive or hypertensive out-of-office BP values. These individuals are considered to be normotensive or hypertensive, but nevertheless still have a considerable “alerting response” or “white-coat effect”.

The use of the term “white-coat”, although it has persisted, is spurious in that the in-office increases in BP are not just in response to the presence of a physician wearing a “white-coat”. Increased in in-office BP are likely to occur as a consequence of a number of effects that may differ from person-to-person, such as anxiety in response to the presence of the observer irrespective of whether they are a physician or wearing a white coat (the observer will determine whether they are healthy or not), anxiety in response to the medical environment itself if busy and overwhelmingly representative of “negative” connotations (death and sickness), or the impact of the BP cuff inflating (Mancia et al 1996). Hence, a number of alternative terms have been used to identify this effect, including an “alerting response” itself, or “isolated office hypertension”. However, as most clinicians are familiar with the term “white-coat”, this term has tended to be retained by most recognised sources. In the present thesis I will therefore use the terms “white-coat” hypertension, isolated in-office hypertension, “white-coat” effects,

“alerting responses”, and isolated increases in in-office BP interchangeably and where appropriate. Importantly, by recommending that all patients with elevated in-office BP values also have an increased ambulatory day BP before initiating therapy, the new NICE guidelines for the United Kingdom have effectively adopted the approach that “white coat” hypertension should be excluded before therapy is initiated (National Clinical Guideline Centre 2011). The evidence to either support or refute these hypotheses will be provided in the course of the present chapter in section 1.3. Importantly however, there is evidence that the “white-coat” effect is driven by factors that may be of pathological significance. What is this evidence?

The white-coat effect has been shown to be associated with possible sympathetic nervous system activation or a decrease in parasympathetic nervous system activation relative to sympathetic activation (Lantelme et al 1998, Neumann et al 2005), which produces vasoconstriction rather than a tachycardia (Lantelme et al 1998), although these findings have not been reproduced by all studies (Pierdomenico et al 2000). However, in the latter study only 12 patients per group were studied and they did not report on the higher and lower frequency domain components of heart rate variability (HRV) (Pierdomenico et al 2000). In this regard, both HRV domains are required for the appropriate assessment of sympathovagal activity. In addition, the white coat effect may be associated with abnormalities in endothelial function, as assessed from brachial artery endothelium-dependent flow mediated dilatation (Murata et al 2006). The latter effect may however, reflect end organ damage rather than a pathophysiological process involved in contributing toward increases in BP.

1.2.3 Isolated out-of-office or “masked” hypertension

A further clinical entity of concern which can only be detected using out-of-office BP measurement is the presence of elevated day BP values despite the presence of normal in-office BP values. This is called “masked” hypertension, or more appropriately isolated out-of-office hypertension (O’Brien et al 2005, Chobanian et al 2003). The mechanisms that explain why individuals with isolated out-of-office hypertension have normal in-office BP values has not been provided and no hypotheses appear to be forthcoming. As this clinical entity may represent higher day levels of activity, it is nevertheless important to consider the possibility that these individuals are just highly active during the day, a finding that is likely to protect against rather than increase the risk for cardiovascular events. It is therefore possible that isolated out-of-office hypertension (masked hypertension) may not increase the risk of cardiovascular events. The evidence to either support or refute the hypothesis that one reason why out-of-office BP measurements may be better than in-office BP measurements to detect cardiovascular risk is in-part because out-of-office ambulatory BP incorporates the risk attributed to masked hypertension will be provided in the course of the present chapter in section 1.3.

1.2.4 Inappropriate in-office BP measurement

As acknowledged by all guidelines for the measurement of BP (O’Brien et al 2003, Pickering et al 2005), as well as guidelines for the diagnosis and management of hypertension (WHO 2003, Chobanian et al 2003, Williams et al 2004, Mancia et al 2007, Mendis et al 2007, Flack et al 2010, Seedat and Rayner 2012) the referant (“gold standard”) and the preferred in-office BP measurement remains the auscultatory technique at the brachial artery using a mercury sphygmomanometer. The mercury sphygmomanometer is nevertheless likely to be phased out over time because of the

hazards of employing mercury in the measurement device. Although mercury manometry is the preferred method of BP measurement, there are also a number of arguments against the use of mercury manometry other than the potential that the use of mercury may become obsolete in the future. What are these arguments?

There is now considerable evidence to show that in a busy clinical environment, the measurement of brachial BP using mercury sphygmomanometry is infrequently conducted according to guidelines and is often confounded by measurement error (Kay 1998, Bailey and Bauer 1993). Moreover, no standardisation between observers may occur and observers tend to have digit preferences (Keary et al 1998, O'Brien 2003). In addition, care of mercury manometers and infrequent replacement of parts of the manometers or of the manometer itself may occur (McCartney and Crawford 2003, Knight et al 2001). As a consequence, an appropriate meniscus may no longer be formed between the mercury-glass interface thus preventing the ability to accurately read values. Alternatively, leaks in tubing connecting cuff to manometer or bulb may occur thus limiting the possibility that the cuff is deflated at appropriate speeds, leading in-turn to inaccuracies in measurement.

Because of measurement errors using auscultatory approaches, the trend world-wide has been for many caregivers to employ oscillometric automated or semi-automated devices. However, these devices are often not validated and even if they are, they are also subject to poor service conditions. As 24-hour BP measurements require a considerable effort on the part of the service provider and in some settings are very costly, it is possible that out-of-office BP measurement will be performed with considerably more care. As the devices employed for these measurements are generally well validated and the device does not rely on observer error, it is also possible that out-of-office ambulatory BP measurements will be more reliable. Hence, it is important to

consider the possibility that part of the superiority of out-of-office ambulatory over in-office BP measurement in risk prediction may relate to poor in-office measurement.

1.2.5 Other advantages to out-of-office ambulatory BP measurement.

Out-of-office ambulatory BP measurements may afford the practitioner additional advantages when risk predicting using out-of-office ambulatory BP measurements. These are not approaches which explain the superiority of 24-hour ambulatory over in-office BP measurement, and hence these will not be elaborated on, but rather, briefly mentioned. From out-of-office 24-hour BP measurements, the extent to which increases in the morning BP surge occurs may be assessed. In this regard, cardiovascular events often occur in the morning (Muller et al 1985, Elliot et al 1998, Muller et al 1987) when BP increases, a change which may potentially decrease the stability of atheromatous plaque or increase the chances of cerebral bleeds occurring from weakened vessels. However, even in the latest large clinical trials, differing outcomes have been observed with regards to the morning BP surge, with one large study conducted in a number of populations world-wide in 5645 participants, with 611 cardiovascular events, demonstrating an independent relationship (Li et al 2010), whilst another conducted in 3012 never-treated hypertensives with 268 cardiovascular events, failed to show a similar effect (Verdecchia et al 2012). From out-of-office BP measurements, the variability in BP may also be assessed (the standard deviation or coefficient of variation) and recent evidence indicates that this index, which may reflect the extent to which sympathetic activation occurs (Grassi et al 2012), is independently related to cardiovascular outcomes and to target organ changes (arterial stiffness) (Mancia et al 2007, Rothwell et al 2010^a and 2010^b, Mancia 2011, Grassi et al 2012). However, at this point there is little consensus as to the value of this index and further outcome-driven

studies are required before this measurement is likely to be incorporated as part of routine clinical practice.

A further measurement that has more recently been considered, is an index termed the ambulatory arterial stiffness index, defined as 1-slope of the relationship between systolic and diastolic BP. The systolic-diastolic relationship is determined from the range of BP values obtained over the 24-hour period. This index has been shown to be closely correlated with aortic pulse wave velocity (Li et al 2006), the currently accepted referent measure of aortic stiffness, and to cardiovascular outcomes (Dolan et al 2006, Kikuya et al 2007, Hansen et al 2006) and organ damage (Leoncini et al 2006, Ratto et al 2006) independent of 24-hour BP or confounders. However, as this index may not closely reflect arterial stiffness (Schillaci et al 2007) and the ability to accurately assess the slope of the systolic versus diastolic BP relationship depends on the extent to which BP decreases at night (changes which will determine how wide the range of BP values are that can be used to accurately construct the slope of this relationship), the value of this index has been questioned (Schillaci et al 2007).

1.3. Evidence to support the superiority of out-of-office versus in-office ambulatory BP measurement.

What then is the evidence to support the notion that out-of-office ambulatory BP measurements are superior to in-office ambulatory BP measurement? In preceding discussion in sections 1.2.1 to 1.2.4 I have provided a number of possible explanations for out-of-office BP measurement being superior to in-office BP when predicting cardiovascular risk. In the following sections I will therefore discuss the evidence to support the superiority of out-of-office ambulatory BP measurements in the context of these possible mechanisms. The present analysis is not descriptive, but rather is a

critical review of this scientific literature pointing out some areas which require further consideration and the need for additional evidence. Importantly, the present critical analysis is not designed to cast aspersions on the current evidence or on decisions taken by guidelines committees such as the NICE (National Clinical Guideline Centre 2011). Rather, the criticisms levelled at the current evidence are simply to underscore the issues that prompted me to explore the questions that I asked in the current thesis.

1.3.1 Is out-of-office ambulatory BP more closely related to cardiovascular outcomes than in-office BP?

When considering whether to introduce new approaches to clinical practice which have considerable cost or other implications, it is always important to evaluate the level of the current evidence available. In this regard there should be no question that large, well-controlled clinical trials involving interventions provide the highest level of clinical evidence. As such, at the outset it is important to underscore that there is currently no evidence from intervention studies assessing the effect on cardiovascular outcomes when reducing BP to out-of-office ambulatory targets as compared to in-office BP targets. This is likely to be attributed in-part to the fact that thresholds for out-of-office ambulatory BP as derived from outcomes-based studies have only recently been agreed on (Kikuya et al 2007). However, it is also possible that the funds to perform such an intervention study were simply not available either from industry or public sector resources. Notwithstanding this missing evidence, there have nevertheless been a number of excellent large clinical and population-based studies (Perloff et al, 1983, 1989, Ohkubo et al 1994, 2005, Imai et al 1996, Redon et al 1998, Khattar et al 1999, Verdecchia et al, 1994, 1998, 2002, Staessen et al 1999, Robinson et al 2001, Clement et al 2003, Bjorklund et al 2003, 2004, Kikuya et al 2005, Dolan et al 2005, 2009, Fagard

et al 2004, 2008, Hansen et al 2005, Sega et al 2005, Ingelsson et al 2006, Dawes et al 2006, Schwartz et al 2007, Astrup et al 2007, Eguchi et al 2008, Palmas et al 2009, Dzrelinska et al 2009, Mesquita-Bastos et al 2010, Boggia et al 2011) some of which have been summarised in Table 1.1, which have tested the hypothesis that out-of-office BP, as determined from either 24-hour or day ambulatory monitoring, provides prognostic information beyond (independent of or greater than) in-office BP. I have summarised only those studies that have reported more than 50 cardiovascular events and which in the majority of cases also provided hazards ratios for cardiovascular events related to ambulatory and office/clinic BP in separate statistical models (Table 1.1). Those studies cited which failed to provide hazards ratios were deemed sufficiently large to warrant inclusion despite a lack of reporting on hazards ratios.

As indicated in this Table (Table 1.1), the majority of studies provide evidence to indicate that out-of-office ambulatory BP provides prognostic information independent of or greater than in-office BP. What is important to note is that some of these studies report on very large study samples with a significant number of cardiovascular events included in the outcomes (Dolan et al 2005, Dawes et al 2006, Hansen et al 2007, Boggia et al 2011). In addition, these studies have been conducted in a range of settings and important subgroups including in both men and women in the general population (Boggia et al 2011), in the general population at large (Hansen et al 2005, Ingelsson et al 2006) in hypertensives in general (Verdecchia et al 1998, Clement et al 2003, Dawes et al 2006, Mesquita-Bastos et al 2010), or in those with isolated systolic hypertension (Staessen et al 1999), and in groups with pre-existing cardiovascular disease (Fagard et al 2005, Fagard et al 2008). Hence, these studies have provided some fairly convincing

Table 1.1. Summary of important characteristics of large clinical or population-based studies comparing the value of ambulatory (ABP) to office blood pressure (BP) in predicting cardiovascular events. Only studies with more than 50 events per study have been included in the Table.

	Sample size	Population	Number of CV events	Follow-up	ABP superior
Verdecchia et al 1998	2010	Hypertension	200 events	3.8 years	Yes
Khattar et al 1999	688	Referred for hypertension	157 events	9.2 years	Yes
Staessen et al 1999	808	Systolic hypertension	98 events	4.4 years	Yes
Bjorklund et al 2003	570	70 year old men	72 events	8.4 years	Yes
Clement et al 2003	1963	Hypertension	157 events	5.0 years	Yes
Bjorklund et al 2004	872	70 year old men	172 events	9.5 years	No
Pierdomenico et al 2004	1088	Hypertension	55 events	4.7 years	?
Dolan et al 2005	5292	Untreated hypertension	646 events	8.4 years	Yes
Fagard et al 2005	391	With CVD	86 events	10.9 years	Yes
Hansen et al 2005,2006	1700	General	63 deaths/156 events	9.5 years	Yes/Yes
Kikuya et al 2005	1332	General	72 events	10.8 years	Yes
Ohkubo et al 2005	1332	General	Not stated	10.2 years	Yes
Sega et al 2005	2051	General	56 deaths	10.9 years	No
Dawes et al 2006	10 129	General practices	901 deaths	8.2 years	Yes
Ingelsson et al 2006	951	General	70 with heart failure	5 years	Yes
Ben Dov et al 2007	3957	Referred for ABP	303 deaths	14 years	Yes
Hansen et al 2007	7030	Meta-analysis of population -based studies*	863 deaths	9.5 years	Yes
Eguchi et al 2008	1268	Population (301 with DM)	72 events for non-DM 28 events for DM	50±23 months	Yes
Fagard et al 2008	302	With CVD	84 events	6.8 years	Yes
Dolan et al 2009	1905	ASCOT clinical trial in hypertension	239 events	5.5 years	Yes
Mesquita-Bastos et al 2010	1200	Hypertension	152 events	8.2 years	Yes
Boggia et al 2011	4397	Women from meta-analysis* of population-based studies	320 events	11.2 years	Yes
	4960	Men from meta-analysis* of population-based studies	760 events	11.2 years	Yes

ASCOT Anglo-Scandinavian Cardiac Outcomes Trial; DM Diabetes Melitus; ABP Ambulatory Blood Pressure; CV Cardiovascular; CVD, Cardiovascular Disease. *The meta-analyses were conducted on individual patient data.

evidence to show that out-of-office ambulatory BP provides prognostic information independent of in-office BP. Nonetheless, it is important that a careful analysis of all of the data provided by these studies is performed.

The hazards ratios for cardiovascular events or death for the studies comparing the prognostic value of ambulatory out-of-office with in-office BP summarised in Table 1.1 are given in Figure 1.1. There is no question that when comparing hazards ratios that in the majority of studies out-of-office ambulatory BP is superior to in-office BP (Figure 1.1). However, there are some additional features of the data shown that warrant further consideration. First, in one study conducted in 872 elderly (70 years of age) men (Bjorklund et al 2004) and reporting on 172 cardiovascular events, the hazards ratios provided for in-office BP measurement are similar to those for out-of-office ambulatory BP. Although hazards ratios were not provided, a second study conducted in a large population sample also provided good evidence to indicate that conventional BP is prognostically equivalent to ambulatory BP when risk predicting (Sega et al 2005). Thus, the point needs to be raised that in-office BP measurement can provide prognostic information that compares well with out-of-office BP ambulatory measurement. Second, a disconcerting point of many of these studies is the lack of ability of in-office BP measurement values to show a significant ability to predict cardiovascular events (Staessen et al 1999, Fagard et al 2005, Ingelsson et al 2006, Dawes et al 2006, Fagard et al 2008, Mesquita-Bastos et al 2010). This is clearly against the notion of what has been demonstrated on innumerable occasions, too many to list in the present thesis, that in-office BP does predict cardiovascular outcomes. Consequently, in these studies (Staessen et al 1999, Fagard et al 2005, Ingelsson et al 2006, Dawes et al 2006, Fagard et al 2008, Mesquita-Bastos et al 2010) at least the question of how well in-office BP measurements were conducted needs to be considered. In these circumstances, the point also needs to be made that perhaps the superiority of out-of-office BP

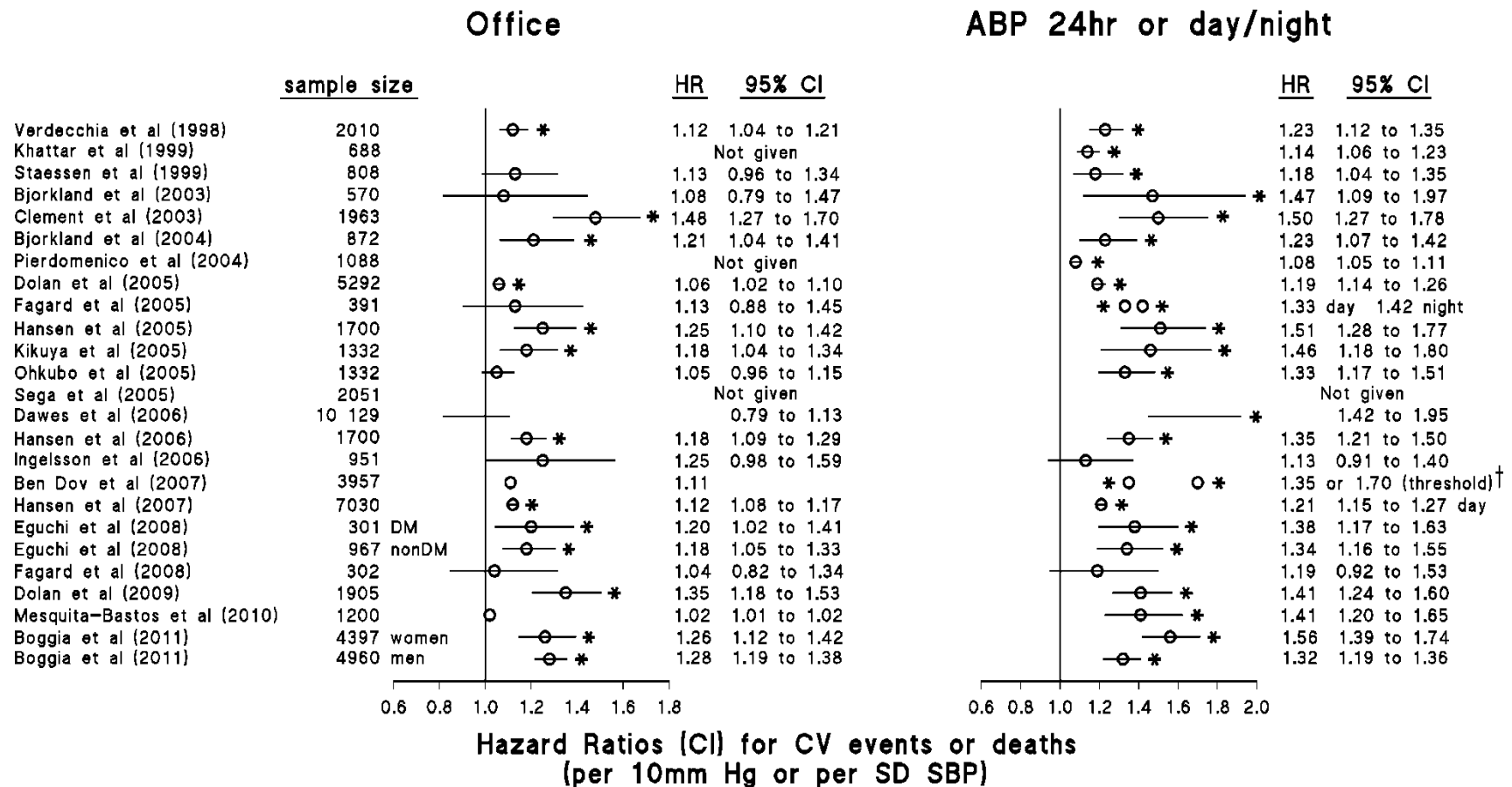


Figure 1.1. Hazards ratios and 95% confidence intervals (CI) for cardiovascular events in large clinical or population-based studies comparing the value of ambulatory (ABP) to office blood pressure (BP). *p<0.005

measurement reflects the inability to standardise in-office BP measurement across centres or to ensure that the BP measurements across centres were well conducted. In this regard, I have attempted to summarise the evidence that may allow one to analyse the methodology, accuracy or reproducibility of in-office BP measurements across centres in these studies. This evidence has been summarised in Table 1.2. What are the conclusions that could be drawn from the evidence provided in Table 1.2?

What is apparent from Table 1.2 is the striking lack of reporting on methodology of in-office BP measurement, approaches employed to ensure that measurements were standardised across observers, or reporting on the quality of in-office BP measurements. The reader is therefore left to assume that in those studies where physicians were measuring BP, that physicians were measuring BP accurately, despite the considerable evidence to show that physicians do not measure BP accurately (Graves et al 2004, Pickering et al 2005); that the alerting responses produced by physicians were comparable with that produced by nurses, despite the considerable evidence to suggest otherwise (Little et al 2002); that despite the fact that in the majority of studies multiple observers were employed, that inter-observer variability assessments were limited; and lastly that rigorous approaches to ensure accurate BP assessments were put into place. In this regard, I could find no data reporting on the quality of BP measurements such as the chances that digit preferences occurred (e.g., the number of times that BP was reported on to the nearest 0 mm Hg); that BP measurements were not missed; the number of times that auscultatory BP values were reported to even instead of odd numbers; and the number of times identical consecutive numbers were provided. Thus, an important limitation of all of these prior studies summarised in Tables 1.1 and 1.2 and Figure 1.1, is that one interpretation for the superiority of ambulatory out-of-office BP as opposed to in-office BP measurements is that in-office BP measurements were not appropriately performed. Does the current evidence support any of the other possible

Table 1.2. Summary of evidence that allows for an analysis of the methods or quality of in-office BP measurement in studies comparing the prognostic value of ambulatory (ABP) to office blood pressure (BP) measurement.

	Sample size	Method	Personnel	Number of observers	Quality reported
Verdecchia et al 1998	2010	Sphgmomanometry	Physicians	Multiple	No
Khattar et al 1999	688	Not stated	Nurses	Not stated	No
Staessen et al 1999	808	Sphygmomanometry	Physicians	Multiple	No
Bjorklund et al 2003	570	Sphygmomanometry	Not stated	Multiple	No
Clement et al 2003	1963	Sphygmomanometry	Not stated	Multiple	No
Bjorklund et al 2004	872	Sphygmomanometry	Not stated	Multiple	No
Pierdomenico et al 2004	1088	Not stated	Not stated	Not stated	No
Dolan et al 2005	5292	Sphygmomanometry/automated	Nurses	Not stated	No
Fagard et al 2005	391	Sphygmomanometry	Physicians	Multiple	No
Hansen et al 2005,2006	1700	Random zero sphygmomanometry	Not stated	Not stated	No
Kikuya et al 2005	1332	Automated	Nurses	Multiple	No
Ohkubo et al 2005	1332	Automated	Nurses	Multiple	No
Sega et al 2005	2051	Sphygmomanometry	Not stated	Not stated	No
Dawes et al 2006	10 129	Sphygmomanometry/automated	Nurses/physicians	Multiple	No
Ingelsson et al 2006	951	Sphygmomanometry	Physicians	Multiple	No
Ben Dov et al 2007	3957	Not stated	Not stated	Not stated	No
Hansen et al 2007	7030	Sphygmomanometry/automated	Nurses/physicians	Multiple	No
Eguchi et al 2008	1268	Not stated	Not stated	Not stated	No
Fagard et al 2008	302	Sphygmomanometry	Physicians	Multiple	No
Dolan et al 2009	1905	Automated	Not stated	Multiple	No
Mesquita-Bastos et al 2010	1200	Sphygmomanometry/automated	Not stated	Not statde	No
Boggia et al 2011	4397	Sphygmomanometry/automated	Nurses/physicians	Multiple	No
	4960	Sphygmomanometry/automated	Nurses/physicians	Multiple	No

Sphygmomanometer, mercury sphygmomanometer. Automated, automated blood pressure device.

reasons given for the superiority of ambulatory out-of-office as opposed to in-office BP measurements for risk prediction?

1.3.2 Does night BP provide prognostic information beyond day BP?

As indicated in previous discussion (section 1.2.1) one reason given for performing out-of-office BP in addition to or in place of in-office BP is that in-office BP does not account for the BP load faced by the cardiovascular system over a 24-hour period. In this regard, the biggest differences in BP occur between day and night BP periods. As previously indicated in section 1.2.1, the decrease in BP during the night as compared to the day, often referred to as “BP dipping”, reflects the combined effect of a number of factors including a reduced activity of the sympathetic nervous system; a system that plays an important role in controlling BP. Thus, there has been considerable interest in the pathophysiological significance of “BP dipping”, resulting in the hypothesis that the difference in day and night BP or the ratio of night/day BP may be an independent predictor of cardiovascular outcomes. What is the evidence to support the notion that night BP provides information beyond day BP when risk predicting or that an attenuated BP dipping predicts risk? In this regard a number of studies have reported on night as compared to or independent of day BP; the role of BP dipping or the impact of increases in BP at night only, when assessing cardiovascular risk (O’Brien et al 1988, Zweiker et al 1994, Verdecchia et al 1994, 1998, 2000, 2007, 2012, Ohkubo et al 1997, 1998, 2002, Yamamoto et al 1998, Nakano et al 1998, 2004, Khattar et al 2001, Clement et al 2003, Bjorklund et al 2004, Sega et al 2005, Staessen et al 1999, Dolan et al 2005, 2009, Fagard et al 2004, 2005, 2008a, 2008b, 2009, Boggia et al 2007, Hansen et al 2005, 2006, 2011, Ingelsson et al 2006, Kario et al 2001, Ben-Dov et al 2007, Astrup et al 2007, Schwartz et al 2007, Brotman et al 2008, Eguchi et al 2008, Ishikawa et al

2008, de la Sierra et al 2009, Fan et al 2010, Kikuya et al 2005, Muxfeldt et al 2009, Palmas et al 2009, Ungar et al 2009, Bouhanick et al 2008, Dzielinska et al 2009, Mesquite-Bastos et al 2010). Many of these studies provide evidence to support the notion that either night BP predicts risk independent of or stronger than day BP; that an attenuation of the extent of decline in BP at night predicts cardiovascular risk; that a higher night than day BP (reversed dipping) independently predicts cardiovascular events; or that an increased night BP predicts risk even when day BP is normal (O'Brien et al 1988, Zweiker et al 1994, Verdecchia et al 1994, 1998, 2000, 2007, 2012, Ohkubo et al 1997, 1998, 2002, Yamamoto et al 1998, Nakano et al 1998, 2004, Clement et al 2003, Sega et al 2005, Staessen et al 1999, Dolan et al 2005, 2009, Fagard et al 2004, 2005, 2008a, 2008b, 2009, Boggia et al 2007, Ingelsson et al 2006, Kario et al 2001, Ben-Dov et al 2007, Astrup et al 2007, Schwartz et al 2007, Brotman et al 2008, Ishikawa et al 2008, de la Sierra et al 2009, Fan et al 2010, Kikuya et al 2005, Palmas et al 2009, Ungar et al 2009, Bouhanick et al 2008, Dzielinska et al 2009, Muxfeldt et al 2009, Mesquite-Bastos et al 2010).

However, because a number of prior studies had either failed to show a worse prognosis associated with a higher nighttime BP independent of day BP (Khattar et al 2001, Eguchi et al 2008, Hansen et al 2006, Bjorklund et al 2004); had failed to show a worse prognosis associated with a higher nighttime BP independent of day BP on continuous analysis (Kario et al 2001); had not adjusted for 24-hour BP (Clement et al 2003, Dolan et al 2009, Palmas et al 2009, Ungar et al 2009); had only demonstrated a relationship in a select subgroup (Astrup et al 2007), or had demonstrated the independent effect on cross-sectional rather than longitudinal analysis, a meta-analysis was conducted on longitudinal data (Hansen et al 2011). In this meta-analysis, nighttime BP was associated with cardiovascular outcomes independent of and stronger than day BP (Hansen et al 2011). The characteristics of the longitudinal studies with more than 50

cardiovascular events that have reported hazards ratios for day and night BP separately are summarised in Table 1.1. The outcomes of these are summarised in Figure 1.2. What are the striking features of these studies?

Although, as indicated in the aforementioned paragraph, many of the studies listed in Figure 1.2 provide evidence to show that night BP provides prognostic information independent of or greater than day BP when risk predicting, it should also be noted that a number of studies show a risk for cardiovascular outcomes that although not statistically stronger is numerically stronger (Clement et al 2003, Bjorklund et al 2004, Hansen et al 2005, Boggia et al 2011 [men]) or at least as strong (Boggia et al 2011 [women], Eguchi et al 2008) for day as it is for night BP. Of importance is that in an individual meta-analysis of many population based studies (Boggia et al 2007), although night BP was noted to be a better predictor of fatal endpoints than day BP, day BP was just as good as night BP for predicting combined fatal and non-fatal cardiovascular events. Consequently, these authors (Boggia et al 2007) suggested that to accurately predict cardiovascular risk, BP measurement should be obtained across the 24 hour BP spectrum.

Although the ability of indices of BP dipping to predict cardiovascular risk have been listed in the aforementioned discussion, a few recent publications warrant further discussion. In 23 856 hypertensives and 9641 individuals from a variety of populations, dipping status, and the night/day ratio has been shown to add little prognostic information beyond 24-hour BP (Hansen et al 2011). Furthermore, in the IDACO study, analysis conducted in 7458 individuals enrolled in population studies world-wide, although the ratio of night/day BP was associated with cardiovascular outcomes independent of 24-hour BP and additional confounders, this relationship was lost after excluding treated participants (Boggia et al 2007). These authors therefore suggested that the ability of indices of “BP dipping” to predict cardiovascular outcomes independent

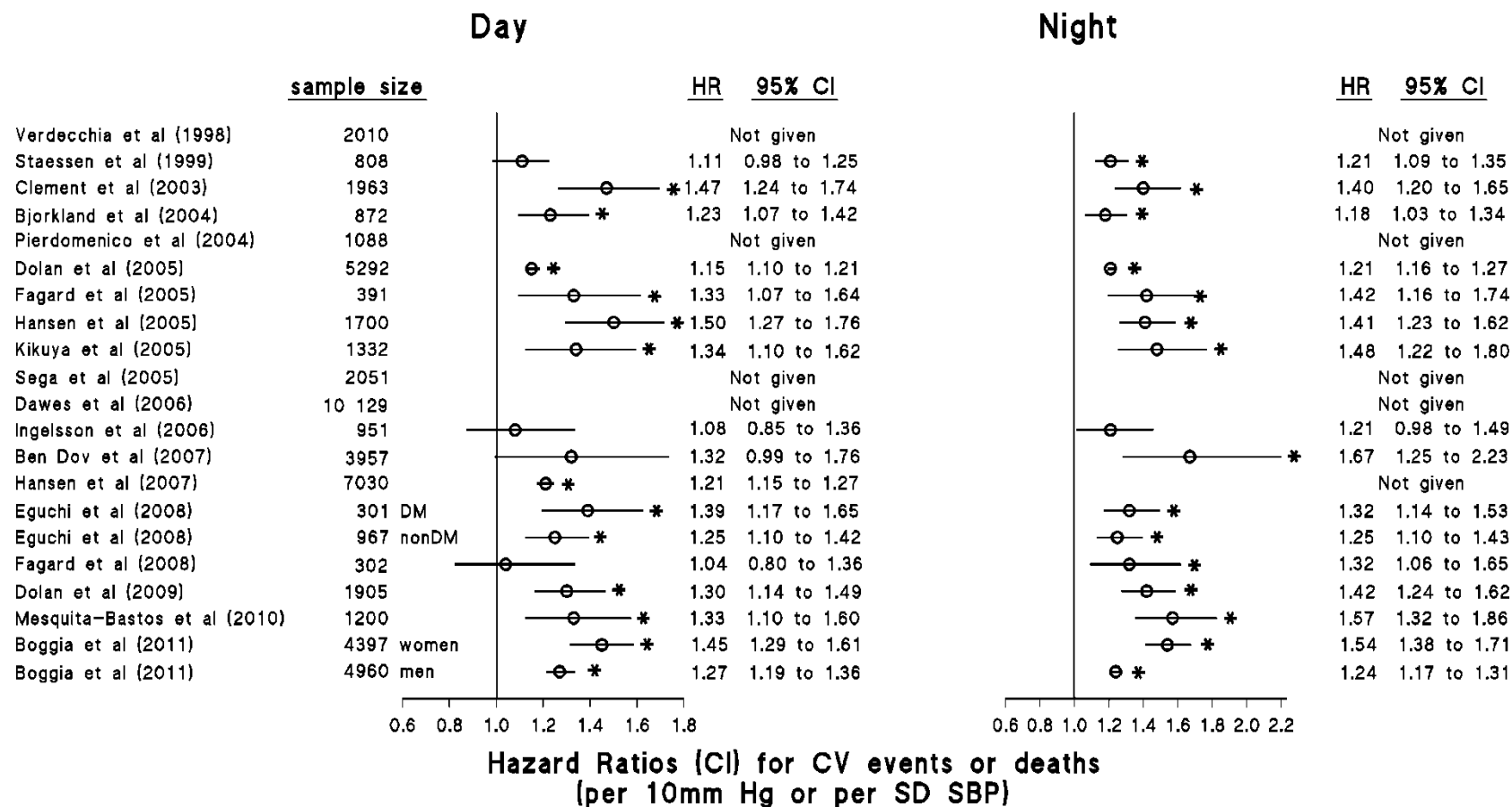


Figure 1.2. Hazards ratios and 95% confidence intervals (CI) for cardiovascular events in large clinical or population-based studies comparing the value of ambulatory night to day blood pressure. * $p < 0.005$

of 24-hour BP may reflect reverse causality. That is, those with a reduced BP dipping are receiving treatment and hence are likely to be at a higher risk (Boggia et al 2007). These authors suggested that antihypertensive treatment taken in the morning will mainly decrease day BP, thus producing a reduced night/day ratio (Boggia et al 2007). However, this explanation does not apply to data obtained in 3012 never-treated hypertensives, where a blunted or reverse dipping pattern was associated with cardiovascular outcomes independent of 24-hour BP and a number of confounders (Verdecchia et al 2012). Clearly, only intervention studies specifically targeting BP dipping or nocturnal BP (lowering BP to nocturnal thresholds) will resolve the issue of the role of BP dipping and night BP beyond day BP in contributing toward adverse cardiovascular effects.

1.3.3 Are “white-coat” and “masked” hypertension prognostically important?

A number of outcome-driven studies have evaluated whether “white-coat” (isolated in-office hypertension) or “masked” (isolated out-of-office hypertension) hypertension have prognostic significance (Khattar et al 1998, Bjorklund et al 2003, Ohkubo et al 2005, Hansen et al 2006, 2007, Mancia et al 2006, Celis et al 2002, Gustavsen et al 2003, Bobrie et al 2004, 2008, Bjorklund et al 2003, Clement et al 2003, Verdecchia et al 1994, 1997, 1998, 2005, Staessen et al 1999, Fagard et al 2000, 2004, 2007, Kario et al 2001, Celis et al 2002, Pierdomineco et al 2004, 2005, Polonia et al 2005). The results of these studies were not necessarily consistent. Indeed, the incidence of cardiovascular events has been reported as being the same in “white-coat” hypertensives as in normotensives in some studies (Verdecchia et al 1994, Kario et al 2001, Pierdomenico et al 2004, Fagard et al 2004, 2005, Polonia et al 2005, Hansen et al 2006), whilst in other studies the incidence of cardiovascular events was greater in

“white-coat” hypertensives as compared to normotensives (Gustavsen et al 2003, Verdecchia et al 2005, Mancia et al 2006). To attempt to resolve this issue a meta-analysis of these studies was conducted (Fagard et al 2007) and in the IDACO study, a meta-analysis of individual data was conducted in 7030 individuals enrolled in population studies conducted world-wide (Hansen et al 2007).

The meta-analyses of published studies provided clear evidence that white-coat hypertension does not carry a statistically significantly greater risk for cardiovascular outcomes as compared to normotensives (adjusted hazards ratios=1.12, confidence intervals=0.84-1.50)(Fagard et al 2007). However, masked hypertension was associated with a statistically significantly greater risk for cardiovascular outcomes as compared to normotensives (adjusted hazards ratios=2.00, confidence intervals=1.58-2.52)(Fagard et al 2007). The risk of cardiovascular outcomes predicted by masked hypertension as compared to normotension was in fact similar to that noted for the risk of sustained hypertension as compared to normotension (adjusted hazards ratios=2.28, confidence intervals=1.87-2.78)(Fagard et al 2007).

With respect to the meta-analysis conducted in individual data, similar findings were noted (Hansen et al 2007). In this regard, white coat hypertension did not carry a statistically significantly greater risk for cardiovascular outcomes as compared to normotensives (adjusted hazards ratios=1.17-1.22, depending on the thresholds for ambulatory BP employed)(Hansen et al 2007). However, masked hypertension was associated with a statistically significantly greater risk for cardiovascular outcomes as compared to normotensives (adjusted hazards ratios=1.44-1.63, depending on the thresholds for ambulatory BP employed)(Hansen et al 2007). The risk of cardiovascular outcomes predicted by masked hypertension as compared to normotension was also similar to that noted for the risk of sustained hypertension as compared to normotension (adjusted hazards ratios=1.77-1.80, depending on the thresholds for ambulatory BP

employed)(Hansen et al 2007). It is therefore possible that the ability of ambulatory out-of-office BP to predict cardiovascular outcomes independent of in-office BP may in-part be attributed to the fact that ambulatory BP accounts for the lack of risk related to white-coat hypertension and the risk related to masked hypertension, effects which would not be recognised by in-office BP measurement alone.

However, as was discussed in section 1.2.2, white-coat hypertension is not the same as white-coat effects. In this regard, statistical analysis of white-coat effects in a categorical manner, such as occurs when comparing data between white-coat hypertensives and normotensives, ignores the possibility that white-coat effects may occur in normotensives and that this may reflect the presence of cardiovascular damage. This issue is further discussed in section 1.3.3.1 below and is in-part an argument that prompted me to perform some of the studies described in the present thesis. The arguments in favour of the hypothesis that generated these studies are provided in section 1.4.

1.3.3.1 Are white-coat effects benign?

As indicated in the preceding section, despite the considerable evidence to indicate that white-coat hypertension is benign, it is important when evaluating whether out-of-office ambulatory BP should become part of routine clinical management to decide whether in-office increases in BP (white-coat effects) should be excluded from clinical management. In this regard, as also highlighted in preceding sections, the assessment of the cardiovascular risk carried by white-coat hypertension, when white-coat hypertension is statistically evaluated as a categorical trait, assumes that a similar alerting response does not occur in normotensive participants. This is indeed not the case as many normotensives also have a considerable in-office alerting response

(alerting effect), but the in-office BP achieved is nevertheless still within normotensive ranges. The question should therefore be whether the alerting response (white-coat effect) is benign? If it is then the “white-coat” component of the increase in BP in patients with white-coat hypertension would carry no excessive risk and every effort should be made to try and exclude those with white-coat hypertension as an “at risk” group. However, if the alerting response (white-coat effect) carries a significant cardiovascular risk, then including the white-coat component of BP in risk assessment by performing in-office rather than out-of-office BP measurements could be considered as part of overall risk assessment. Is there any evidence to suggest that the white-coat effect is pathological in nature?

Although meta-analyses of outcome-driven studies (Hansen et al 2005, Fagard et al 2007) and other studies assessing target organ changes (White et al 1998, Verdecchia et al 1992, Gosse et al 1993, Hoegholm et al 1993, Cavallini et al 1995, Pierdomenico et al 1995, 2002) suggest that white-coat hypertension is benign, some studies assessing either cardiovascular outcomes or target organ damage nevertheless suggest a pathological role (Cardillo et al 1993, Weber et al 1994, Kuwajima I et al 1993, Bidlingmeyer et al 1996, Glen et al 1996, Soma et al 1996, Muscholl et al 1998, Owens et al 1998, Palatini et al 1998, Lantelme et al 1998, Landray et al 1999, O’Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Sega et al 2001, Gustavsen et al 2003, Verdecchia et al 2005, Mancia et al 2006). In addition, the white-coat effect is strongly and independently related to an attenuated decline in BP at night (Bochud et al 2009) and as indicated in preceding discussion, night BP is related to cardiovascular outcomes independent of day BP (section 1.3.2). Furthermore, in participants with white-coat hypertension, a blunted nocturnal decrease in BP is associated with organ damage (Turfaner et al 2009). Moreover, when assessing the impact of the alerting response as determined using continuous rather than categorical analysis, by employing the

calculation of office minus day BP, the alerting response is strongly associated with organ damage (Palatini et al 1997). It is therefore possible that white-coat effects are not benign. However, in this regard, there are a number of questions which remain unanswered.

Alternative studies (Gosse et al 1993) have not reproduced the findings that office minus day BP is independently associated with organ damage (Palatini et al 1997). Moreover, the alerting response may only be related to organ damage at higher (hypertensive) BP values (Palatini et al 1997). If the alerting response is only important at higher BP values, then it is unlikely to be an important cause of cardiovascular damage within normotensive BP ranges and hence its presence should be excluded from risk assessment. Furthermore, the use of office-day BP, as a surrogate of the alerting response, has been discredited because of inverse associations with day BP, and a lack of relationship with office minus day diastolic BP or pulse rate (Parati et al 1998), changes which should occur if office minus day systolic BP were to reflect a sympathetic response. Thus, it is presently uncertain as to whether the white-coat effect or alerting response is an important response which should or should not be excluded from risk assessment. Clearly, further evidence is required before deciding on whether the white-coat effect should (by performing out-of-office measurements) or should not be excluded from risk assessment. This is a particularly important question in settings where out-of-office ambulatory BP measurements are unlikely to become part of routine clinical assessment because of the costs of the devices required to perform the measurement. In this regard, as previously indicated, in the South African setting nurses are largely responsible for primary prevention programmes. Whether the white-coat effect elicited by nurses, which as shall be described in later sections (1.4.2) is considerably lower than that elicited by physicians, is associated with cardiovascular damage is unknown. Therefore, in the present thesis I explored the question of whether

the white-coat effect elicited by nurse BP measurement (nurse office-day) BP suffers from the same limitations as a surrogate of the alerting response as previously described and if not, whether the nurse elicited white-coat effect is benign even within normotensive ambulatory BP ranges. The arguments that underpin the hypothesis that I have proposed are outlined in section 1.4.2 below. The data and the implications thereof are discussed in chapter 3 of the present thesis.

1.3.3.2 Should pathological effects of white-coat responses be treated with antihypertensive therapy?

As suggested by the recent NICE guidelines (National Clinical Guideline Centre 2011), white-coat hypertension is not an entity that should be treated with antihypertensive therapy. Although this decision is largely based on the dominant evidence to show that white-coat hypertension is not associated with cardiovascular outcomes beyond that for sustained normotension, as indicated in the previous section, white-coat effects may be pathological. Hence it would not be unreasonable to suggest that in circumstances where ambulatory BP measurement cannot be performed due to cost implications, that antihypertensive treatment may not be unwarranted. In other words, why perform ambulatory BP monitoring when those with white-coat hypertension could benefit from antihypertensive therapy? Importantly, the costs of ambulatory BP monitoring and the infrastructure required, are greater than those of antihypertensive therapy. The key question in this regard is whether there is sufficient evidence to suggest that white-coat hypertensives would benefit from BP lowering therapy? In other words, is there evidence to support a role for BP in mediating the potential pathological effects of white-coat hypertension.

One argument to support the use of antihypertensive therapy in white-coat hypertensives, is that these individuals have relatively consistently been demonstrated to have an ambulatory BP that is higher than that of persons with sustained normotension (Fagard et al 2007, Mancia et al 2006). In addition, as indicated in the aforementioned discussion (1.3.3.1), the white-coat effect is strongly and independently related to an attenuated decline in BP at night (Bochud et al 2009) and night BP is related to cardiovascular outcomes independent of day BP (section 1.3.2). Thus, there is some argument to suggest that the excess cardiovascular outcomes associated with white-coat hypertension in some studies (Gustavsen et al 2003, Mancia et al 2006, Verdecchia et al 2005) may be attributed to BP effects. If so, it is possible that antihypertensive therapy may benefit even those with white-coat hypertension. However, currently there are no studies that have evaluated whether the relationship between white-coat effects and organ damage can be attributed to an attenuated decrease in BP at night. As in the present thesis I was able to show an independent relationship between white-coat effects and organ damage (chapter 3), as part of the present thesis I also explored the question of whether this relationships can be attributed to an attenuated decrease in nocturnal BP. The arguments that underpin the hypothesis that I have proposed are outlined in section 1.4.2 below. The data and the implications thereof are discussed in chapter 4 of the present thesis.

Although there is some evidence to indicate that white-coat effects may be pathological and that this could be attributed to a higher ambulatory BP, no studies have been performed to assess whether those with white-coat hypertension have reduced cardiovascular outcomes when receiving antihypertensive therapy. There are nevertheless studies that have evaluated whether reductions in white-coat effects with antihypertensive therapy are associated with improvements in BP-related target organ changes. In this regard, two studies have reported that decreases in the difference

between office and day BP produced by antihypertensive therapy (white-coat effects) are unrelated to improvements in organ damage (Fagard et al 2000, Paratti et al 2000). Thus, even if white-coat hypertension or effects were pathological, there is considerable uncertainty as to whether these effects could be effectively targeted by antihypertensive therapy. In this regard, as indicated in the aforementioned section (1.3.3.1) of the present thesis, I evaluated whether nurse-derived BP measurement, which elicits a considerably lower white-coat effect than physicians, was associated with cardiovascular damage independent of BP. As shall be described in chapter 3, despite demonstrating a mean white-coat effect (nurse office-day BP value) comparable with other studies demonstrating a markedly lower nurse-elicited white-coat effect (see section 1.4.2 and chapter 3 for further details), I nevertheless demonstrated a relationship between nurse office-day BP and organ damage, with markedly different ambulatory BP-independent differences noted in the highest versus the lowest quartile of nurse office-day BP. Thus, even in circumstances where white-coat effects are not as marked as would normally be expected, such as when nurses perform the measurement, white-coat effects have marked pathological significance independent of ambulatory BP. The question therefore arises as to whether antihypertensive therapy modifies the nurse-derived white-coat effect and whether this translates into a decrease in cardiovascular damage. To address this question, in the present thesis I evaluated whether antihypertensive therapy modifies nurse-derived white-coat effects in hypertensives and whether this either translates into an impact on target organ changes or whether nurse-derived white-coat effects predict an inability to regress target organ changes. The arguments that underpin the hypothesis that I have proposed are further outlined in section 1.4.2 below. The data and the implications thereof are discussed in chapter 5 of the present thesis.

1.4 Implications of the superiority of out-of-office as compared to in-office BP measurements for economically developing populations of African descent.

As indicated in previous discussion it is unlikely that out-of-office ambulatory BP will be introduced for routine risk assessment in economically underdeveloped or developing communities because of the costs of the devices to perform these measurements. When considering the possible BP measurements that may act as a reasonable alternative to out-of-office ambulatory BP measurements, the explanation for the superiority of out-of-office ambulatory over in-office BP measurements for risk prediction require consideration. These reasons have largely been summarised in preceding sections with the evidence either for or against these hypotheses provided. To recapitulate however, these include the inability of in-office BP measurements to closely represent BP control at night; the inability of in-office BP measurements to exclude white-coat or isolated in-office hypertension, or white-coat effects *per se*, without out-of-office BP measurements; the possibility that the white-coat effect as opposed to white-coat hypertension is benign; and the inability to identify masked or isolated out-of-office hypertension with in-office BP measurements alone. In the following section, I will discuss each of these issues in turn in the context of what is relevant regarding economically developing communities of African descent in South Africa, the dominant ethnic group in this country.

1.4.1 Night BP in groups of black African ancestry

A meta-analysis of a number of small studies has provided some evidence that in groups of African ancestry, out-of-office ambulatory BP values may be higher than

other populations for a given level of in-office BP because of attenuated decreases in BP at night (Profant and Dimsdale 1999). In a subsequent large, prospective study where out-of-office 24-hour BP was repeatedly and prospectively measured over a number of years in large samples of African-American and European-American youth up until adulthood, provided clear evidence that African-Americans develop a higher BP, mainly at night, in both males and females as compared to European Americans (Wang et al 2006). Furthermore, in the dietary approaches to stop hypertension (DASH) study, African-Americans were noted to have an attenuated decrease in BP at night (Jehn et al 2008). The potential mechanisms that may explain a blunted nocturnal decrease in BP in groups of African descent is through a decreased sleep quality and an attenuation of the decline in sympathetic activity during the night (Sherwood et al 2011). As indicated in previous discussion (section 1.3.2), night BP is at least as important as day BP, and in some instances may be more important when assessing cardiovascular risk. Thus, in-office BP measurements in populations of black African ancestry may not closely reflect the extent of cardiovascular risk attributed to increases in BP. These findings have important implications for our understanding of the impact of BP control at a population or community level on potential future cardiovascular events. What are these implications?

Groups of African ancestry have been reported to have a considerably worse BP control than other ethnic groups (Hertz et al 2005, Cutler et al 2008, Steyn et al 2008). However, these control rates have been estimated from in-office BP measurements. As thresholds for out-of-office ambulatory BP control account for lower out-of-office BP values as compared to in-office BP values (Kikuya et al 2007), in surveillance studies one may expect in-office BP control rates to closely reflect out-of-office ambulatory BP control rates. However, if night BP values are markedly greater for a given in-office BP, in-office BP measurements in this ethnic group may considerably underestimate

prevalence rates of an uncontrolled BP. As a consequence of the uncertainty as to the extent to which actual BP control, as estimated from out-of-office ambulatory BP measurements exists in developing communities of African ancestry, as part of the present thesis I therefore assessed 24-hour, day and night ambulatory BP control and compared these control rates with in-office BP control rates. These data and the implications thereof are described in chapter 2 of the present thesis.

As in chapter 2 I demonstrated that night BP control was markedly worse than day BP control in an urban, developing community of African ancestry, an important question which arose from these findings was whether this translates into organ damage independent of day BP. In the present thesis I therefore also evaluated whether night BP or indices of BP “dipping” are independently associated with target organ damage in this community sample. These data and the implications thereof are described in chapter 4 of the present thesis.

1.4.2 “White-coat effects” in groups of African ancestry in Africa

Whether “white-coat” hypertension has particularly important public health consequences in developing communities of African descent in Africa has not been evaluated. If there is indeed a high prevalence of “white coat” hypertension, then the question of whether the “white coat” effect incorporated in in-office BP measurement is of pathological significance requires consideration. When assessing these questions, it is also important to ensure that in-office BP measurements are appropriate. As highlighted in section 1.3.1 an important potential reason for the superiority of out-of-office ambulatory as compared to in-office BP measurements in risk predicting, may be attributed, in-part to inappropriate methodology employed in many of these studies to assess in-office BP. In this regard, nurses record auscultatory BP with fewer errors, with

lower values than physicians and with less of an alerting response than physicians (Veerman et al 1993, Graves et al 2004, Pickering et al 2005, Little et al 2002). Thus, when comparing in-office to out-of-office ambulatory BP effects on cardiovascular damage, it is important that in-office BP measurements are acquired by well-trained nurses and that inter-observer variability is not an issue. This approach is of particular relevance to South African communities where nurse-controlled primary health care clinics are the mainstay of healthcare for uncomplicated hypertension. Consequently, in the present thesis I also examined whether “white coat” effects are prevalent in an urban, developing community of African ancestry and employed nurse-derived in-office auscultatory BP measurements to assess this question. These data and the implications thereof are described in chapter 2 of the present thesis.

As in the study described in chapter 2 I noted a high prevalence of white coat effects in this community as detected using nurse-derived in-office BP, in chapter 3 of the present thesis I subsequently evaluated whether white coat effects, as assessed from nurse derived office minus day BP (a continuous measurement of a nurse elicited white coat effect) suffer from the same limitations as a surrogate of an alerting response as that previously described for other studies (Parati et al 1998). In this regard, as indicated in section 1.3.3.1 above, previous studies have demonstrated that office-day BP is inversely associated with day BP, and is not related to office minus day diastolic BP or pulse rate (Parati et al 1998), changes which should occur if office minus day systolic BP were to reflect a sympathetic response. Having established that nurse-office-day BP BP is not inversely associated with day BP, and is related to office minus day pulse rate, in this same chapter (chapter 3) of the present thesis, I subsequently report on the relationships between nurse office-day BP and cardiovascular target organ changes independent of ambulatory BP and whether these relationships occur only at

high BP values or even at normotensive ambulatory BP ranges. The implications thereof are also described in chapter 3 of the present thesis.

As in chapter 3 of the present thesis I show that alerting responses (white coat effects) as elicited by nurses indeed have pathological significance even after adjustments for ambulatory BP, the obvious question which arose from this study is whether this effect is indeed truly independent of the adverse effects of BP? In this regard, in a subsequent study in the present thesis I first attempted to assess whether this effect can be explained by relationships with an attenuated nocturnal BP dipping. As pointed out in section 1.3.3.1 above, white coat effects have previously been shown to be inversely associated with nocturnal decreases in BP at night (Bochud et al 2009), and night BP values provide prognostic information beyond day BP (see section 1.3.2). However, there are currently no studies that have evaluated whether the relationship between white coat effects and cardiovascular damage may be explained by an attenuated decline in nocturnal BP. In the present thesis I therefore evaluated whether nurse office-day BP (nurse elicited alerting response) is associated with nocturnal decreases in BP and whether an attenuated nocturnal decline in BP can therefore explain the independent relationship between nurse office-day BP and cardiovascular target organ damage. These data and the implications thereof are described in chapter 4 of the present thesis.

As indicated in previous discussion above (section 1.3.3.2), to be truly certain as to whether white-coat responses reflect pathological changes through BP-related effects, it is important to understand whether these changes are influenced by BP-lowering therapy and whether antihypertensive therapy-induced decreases in white-coat effects translate into an attenuation of target organ changes. Although previous studies suggest that BP-lowering therapy does decrease office-day BP differences, these changes failed to translate into improvements in organ damage (Fagard et al 2000, Paratti et al 2000).

However, it is uncertain whether office-day BP in previous studies (Fagard et al 2000, Parati et al 2000) suffered from the same limitations as a surrogate of an alerting response as that previously described for other studies (Parati et al 1998). Whether nurse-elicited white-coat effects, which as demonstrated in chapter 3, do not suffer from the same limitations as previously described (Parati et al 1998) can be modified by antihypertensive therapy and whether these changes translate into improvements in target organ changes has not been addressed. Thus, in the present thesis I also evaluated whether nurse-office-day BP may or may not be influenced by antihypertensive therapy and if so whether these changes correlate with the regression of left ventricular mass index induced by antihypertensive therapy. These data and the implications thereof are described in chapter 5 of the present thesis.

1.4.3 “Masked hypertension” in groups of African ancestry in Africa

Whether “masked” or isolated out-of-office hypertension has particularly important public health consequences in developing communities of African descent in Africa has not been evaluated. In the present thesis I therefore also evaluated whether a high prevalence of “masked” hypertension exists in an urban developing community of African ancestry. These data and the implications thereof are described in chapter 2 of the present thesis.

1.5 Aims

In summary therefore, in the present thesis:

a) I aimed to assess the control of BP with ambulatory as compared to nurse-derived conventional BP in an urban, developing community of African ancestry in order to ascertain the extent to which a reduced nocturnal as compared to daytime BP control occurs; whether a high proportion of the community have a poor in-office as compared to out-of-office BP control (white-coat or isolated in-office hypertension); and whether a high proportion of the community have a poor out-of-office as compared to in-office BP control (isolated out-of-office or masked hypertension). These data and the implications thereof are presented in chapter 2 and have been published in-part in the *American Journal of Hypertension* (Maseko et al 2010).

b) I aimed to identify whether nurse-derived BP measurements suffer from previously described limitations when employed as an index of an in-office white-coat effect (office-day BP) and the extent to which a nurse-elicited white-coat effect is associated with target organ damage independent of ambulatory BP. These data and the implications thereof are presented in chapter 3.

c) I aimed to determine the extent to which the relationships between nurse-elicited white-coat effects and organ damage may be explained by the high prevalence of uncontrolled nocturnal as compared to day BP values or an attenuated nocturnal decline in BP. These data and the implications thereof are presented in chapter 4.

d) I aimed to determine whether nurse-elicited white-coat effects are decreased by antihypertensive therapy and whether this is either associated with regression of left ventricular mass index or whether nurse-derived isolated increases in in-office BP predict an inability to regress increases in left ventricular mass index. These data and the implications thereof are presented in chapter 4.

CHAPTER 2

Marked Underestimation of Blood Pressure Control with Conventional Versus Ambulatory Measurements in an Urban, Developing Community of African Ancestry.

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Abstract

As groups of African descent may have higher nocturnal blood pressures (BP) for a given day BP than other ethnic groups, I ascertained whether this translates into differences in conventional (CBP) and 24-hour ambulatory (ABP) BP control at a community level. Ambulatory 24-hour, day and night BP (SpaceLabs, model 90207) and CBP (mean of 5 values) control rates were determined in 689 randomly selected participants (>16 years) of African ancestry in South Africa. Of the participants 45.7% were hypertensive and 22.6% were receiving antihypertensive medication. More participants had uncontrolled BP at night (34.0%) than during the day (22.6%, $p<0.0001$). Uncontrolled CBP was noted in 37.2% of participants, while a much lower proportion had uncontrolled ABP (24.1%)($p<0.0001$). Marked differences in the proportion of hypertensive participants with uncontrolled CBP and ABP were noted (treated: CBP=62.2%, ABP=33.3%, $p<0.0001$; all: CBP=81.3%, ABP=44.4%, $p<0.0001$). These differences were accounted for by a high prevalence of isolated increases in CBP (white-coat effects)(treated=35.9%; all=39.4%). Indeed, after censoring data from participants with white-coat effects, similar CBP and ABP control rates were noted. In conclusion, in communities of African descent, despite a worse BP control at night than during the day, a high prevalence of white-coat effects translates into a striking underestimation of BP control in hypertensives when employing CBP rather than ABP measurements.

2.1 Introduction

Although there is a close relationship between conventional blood pressure (CBP) and cardiovascular disease (Lewington et al 2002, O'Donnell et al 2010), surveillance studies (Hertz et al 2005, Cutler et al 2008, Wang et al 2007, Wolf-Maier et al 2004, Steyn et al 2001, Steyn et al 2008) suggest that CBP control rates are far below acceptable standards and that these control rates may be worse in groups of African ancestry (Hertz et al 2005, Cutler et al 2008, Steyn et al 2008). Nevertheless, as outcome-driven thresholds for ambulatory BP (ABP) have only recently been reported on (Kikuya et al 2007) at the time of conducting the present study no consideration had yet been given to ABP control rates at a population level. In this regard, as compared to CBP measurements, ABP measurements have a number of advantages including the exclusion of measurements obtained during transient rises in BP in the medical environment (white-coat effects) (O'Brien et al 2003). Thus, in population-based studies, ABP predicts cardiovascular outcomes better than CBP (Ohkubo et al 2005, Kikuya et al 2005, Hansen et al 2005, Bjorklund et al 2003, Hansen et al 2007).

Outcome-based studies have derived thresholds for ABP (Kikuya et al 2007) that are considerably lower (130/80 mm Hg) than thresholds for CBP (140/90 mm Hg). As thresholds for ABP control account for lower ABP values as compared to CBP values, in surveillance studies one may expect CBP control rates to closely reflect ABP control rates. However, in some populations, particularly groups of African ancestry, ABP values may be higher than other populations for a given level of CBP because of attenuated decreases in BP at night (Wang et al 2006, Profant and Dimsdale 1999). Thus, CBP measurements in these populations may not closely reflect the extent of cardiovascular risk attributed to increases in BP. To derive a more accurate assessment of the cardiovascular risk produced by an uncontrolled BP at a community level in groups of

African descent, in the present study ABP control rates were assessed and compared with CBP control rates in an urban, developing community in Africa.

2.2 Methods

2.2.1 Study group.

The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69). The study was conducted according to the principles outlined in the Helsinki declaration. Participants gave informed, written consent. The study design has recently been described (Woodiwiss et al 2009, Norton et al 2008, Woodiwiss et al 2008, Libhaber et al 2009, Redelinghuys et al 2010). Nuclear families (either both parents and at least one sibling or one parent and two or more siblings) of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. Street names and addresses of households from formal dwellings represented in the 2001 census were obtained from the Department of Home Affairs. These households were allocated numbers and numbers were selected from a random number generator. People residing in informal dwellings or institutions/homes were not recruited. No subjects of mixed, Asian, or European ancestry were recruited and no Khoi-San subjects were recruited. Of the 620 households approached, nuclear families from 351 households agreed to participate (56.6%). Of the 1029 participants sampled up until November 2010, 689 (67%) had 24-hour ABP values that met with pre-specified quality control criteria (longer than 20 hours and more than 10 and 5 readings for the computation of day and night

means, respectively). Of these participants 556 had CBP measurements performed at home.

2.2.2 Demographic and clinical data

A questionnaire was administered to obtain demographic and clinical data. In order to avoid translational errors, the questionnaire was not translated into an African language, but study assistants familiar with all languages spoken in SOWETO and who either previously lived in SOWETO or currently reside in SOWETO assisted with the completion of each questionnaire. Nevertheless, the majority of participants were reasonably proficient in English. Only same sex assistants were used to assist each family member with the completion of the questionnaire. Assistance was only provided when requested. Study assistants first visited homes of subjects that agreed to participate in the study in order to familiarise participants with the questionnaire. The questionnaire was only completed at a subsequent clinic visit and then ambiguities checked by performing a follow-up home visit. If family members were absent at follow-up home visits, data were checked with them personally via telephonic conversations whenever possible. Ambiguities in answers to the questionnaire were detected by an independent observer prior to a second home visit. A pilot study was conducted in 20 participants to ensure that data obtained in the questionnaires were reproducible when obtained with the assistance of two separate study assistants.

The questionnaire requested specific answers to date of birth, gender, previous medical history, including the presence of hypertension, diabetes mellitus and kidney disease, previous cardiovascular events, including stroke, myocardial infarction or heart failure, the presence of angina pectoris, prior and current drug therapy (analgesic, antihypertensive use [drugs used to lower BP] and glucose lowering agents included),

smoking status (including the number of cigarettes smoked in the past and at the present time), daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity), caffeine consumption (number of cups of tea or coffee and whether they are decaffeinated and the number of cola's a day), exercise frequency and family history of hypertension. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Most of the questions simply required a "yes"- "no" answer, but understanding was assessed by requesting some short answers. If participants were unable to provide the name of medication taken these were obtained on a second home visit.

Height, weight, waist circumference (WC), and sub-scapular and triceps skin-fold thickness (Harpender callipers) were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥ 25 kg/m² and obese if their BMI was ≥ 30 kg/m². Central obesity was defined as an enlarged WC (≥ 88 cm in women and ≥ 102 cm in men) (Third report of the National Cholesterol Education Program (NCEP) expert panel, 2002). Mean skin-fold thickness was calculated as the mean of sub-scapular and triceps skin-fold thickness values. Standard laboratory blood tests of renal function, liver function, haematological parameters, and percentage glycated haemoglobin (HbA_{1c}) were performed. Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or a glycated haemoglobin (Roche Diagnostics, Mannheim, Germany) value $> 6.1\%$ (Bennett et al 2007). Menopausal status was confirmed with measures of follicle stimulating hormone. Dyslipidemia was defined as a total cholesterol > 6.5 mmol/l, LDL cholesterol > 4.0 mmol/l, HDL cholesterol < 1.2 mmol/l in females and HDL cholesterol < 1.0 mmol/l in males. An elevated serum creatinine concentration was defined as ≥ 107 μ mol/l for females and ≥ 115 μ mol/l for males.

2.2.3 Blood pressures

2.2.3.1 Conventional BP.

High quality nurse-derived conventional BP measurements were obtained by a trained nurse-technician according to the European Society of Hypertension and the American Heart Association recommendations using a standard mercury sphygmomanometer (O'Brien et al 2003, Pickering et al 2005) in the office on the same day as the 24-hour ABP measurement in all participants and at home two weeks prior to the office visit in 556 participants. Blood pressure was recorded to the nearest 2 mm Hg. Korotkov phases I and V were employed to identify systolic and diastolic BP respectively and care was taken to avoid auscultatory gaps. Blood pressure was measured 5 times consecutively, at least a minute apart, using appropriate sized cuffs after the subjects had rested for 5-10 minutes in the sitting position. Nurse-derived in-office BP measurements were obtained between 09:00 and 12:00 hours and nurse-derived home BP measurements were obtained between 09:00 and 21:00 hours. The same approach was employed to determine BP in-office and at home. The average of the five recordings was taken as the conventional BP. Only 1% of visits had fewer than the planned BP recordings. The frequency of identical consecutive recordings was 0.14% for systolic BP and 1.74% for diastolic BP. The occurrence of BP values recorded as an odd number was 0.01 %. Of the systolic and diastolic BP readings, 29% ended on a zero (expected =20%).

2.2.3.2 Ambulatory BP.

Twenty-four-hour ambulatory BP monitoring was performed on the same day as nurse-recorded BP measurements using oscillometric monitors (SpaceLabs, model 90207), of which the calibration was checked monthly against a mercury manometer. The size of the cuff was the same as that used for conventional BP measurements. The monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 hours and at 30-minute intervals from 22:00 to 06:00 hours. Subjects kept a diary card for the duration of the recordings to note the time of going to bed in the evening and getting up in the morning. To account for the lifestyle of the community studied (Li et al 2005), day and night periods were analyzed using two methods. First, I defined these periods according to the diary cards in combination with statistical analysis of the transition periods obtained from the mean of actual BP recordings, as ranging from 09:00 to 19:00 hours and from 23:00 to 05:00 hours, respectively. These fixed clock-time intervals were defined in order to eliminate the transition periods (evening and morning) during which BP changes rapidly in most subjects, and in the present study resulted in day and night BP values which varied by only 1-2 mm Hg from the actual out-of-bed and in-bed BP values. Second, I used the diary cards to identify out-of bed (day) and in-bed (night) values. No subjects reported on daytime “naps”. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings (Fagard et al 1996). The average ($\pm$ SD) number of BP recordings obtained was 62.8 ± 11.4 (range=24-81) for the 24-hour period. The average ($\pm$ SD) number of BP recordings obtained was 61.2 ± 12.0 (range=24-81) for the 24-hour period, 28.9 ± 7.1 (range=11-41) for the day and 9.4 ± 1.0 (range=6-11) for the night.

2.2.4 Data analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Data are shown as mean $\pm$ SD unless otherwise specified. Thresholds for ABP were defined as recently demonstrated from outcomes-based studies (Kikuya et al 2007) as $\geq 130/80$ mm Hg for 24-hour BP, $\geq 140/85$ mm Hg for day BP and $\geq 120/70$ mm Hg for night BP. As previous guidelines have advocated day thresholds of $\geq 135/85$ mm Hg (O'Brien et al 2005) as opposed to $\geq 140/85$ mm Hg, in secondary analysis day BP control was also assessed using a threshold of $\geq 135/85$ mm Hg. In order to identify isolated increases in CBP (white-coat effects) and isolated increases in ABP (masked effects), ambulatory hypertension was defined as a day BP of $\geq 135/85$ mm Hg (Hansen et al 2007). Proportions of participants with uncontrolled BP were compared by χ^2 analysis. Multiple logistic regression analysis was used to explore the association between study factors and the presence of white coat hypertension. Multivariate analysis of variance was used to determine the impact of uncontrolled CBP or ABP on target organ changes.

2.3 Results

2.3.1 General characteristics of the participants.

The demographic and clinical characteristics of those with and without ambulatory BP measurements that met with prespecified quality control criteria are shown in Table 2.1. As it was more frequently difficult to obtain high quality ambulatory 24 hour BP recordings in obese participants, those without 24-hour measurements that met with prespecified quality control criteria were more obese and these participants had

Table 2.1. Demographic, anthropometric, clinical and haemodynamic characteristics of those with or without ambulatory blood pressure (ABP) data that met with prespecified quality control criteria.

	With (n=689)	Without (n=340)
% Female	64.4	67.9
Age (years)	43.9±18.1	43.9±18.9
Body mass index (kg/m ²)	28.9±7.7	30.5±8.6**
% Overweight/obese	24.2/39.9	21.2/47.6*
Waist circumference (cm)	89.1±15.5	91.7±17.6*
Regular tobacco intake (%)	14.4	15.0
Regular alcohol intake (%)	21.6	22.6
% with DM or an HbA _{1c} >6.1%	23.5	21.5
Total/HDL cholesterol	3.50±1.30	3.60±2.95
% Hypertensive	45.7	47.0
% Treated for hypertension	22.6	25.3
Nurse office SBP/DBP (mm Hg)	129±22/84±12	132±24/85±13

DM, diabetes mellitus; HbA_{1c}, glycosylated haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure. *p<0.05 **p<0.005 vs with.

a trend for a higher systolic BP (SBP) ($p=0.053$). In general, more women than men participated, a high proportion of participants were obese or had hypertension or diabetes mellitus/HbA1c > 6.1%.

Table 2.2 gives the general characteristics of normotensive participants, hypertensives receiving therapy, and untreated hypertensives. Table 2.3 gives the CBP and ABP values of normotensive participants, hypertensives receiving therapy, and untreated hypertensives. In general hypertensives were older, more were obese, more had more diabetes mellitus/HbA1c>6.1% and more women were postmenopausal (Table 2.2). Nurse recorded SBP and diastolic (DBP) BP values were higher than day SBP and DBP values (Table 2.3). Moreover, day SBP and DBP values were higher than night BP values (Table 2.3).

Of the treated hypertensives ($n=156$), 67.9% ($n=106$) were receiving monotherapy, 88.5% ($n=138$) thiazide diuretic agents, 67.4% ($n=93$) thiazide diuretic monotherapy (hydrochlorothiazide), 18.0% ($n=28$) angiotensin-converting enzyme inhibitors (enalapril or perindopril), 10.3% ($n=16$) long acting calcium channel blockers, and 1.3% ($n=2$) selective β_1 -adrenergic receptor blockers. All of these agents were taken once daily in the morning.

2.3.3 Night versus day BP control.

Irrespective of whether assessed in all participants, treated hypertensives, or all hypertensives, the proportion of participants with uncontrolled night BP was higher than the proportion with an uncontrolled day BP (Figure 2.1). These differences in control rates were noted in men and women, obese and non-obese, in non-smokers as well as for systole and diastole (Table 2.4). The prevalence of participants with an uncontrolled night, but normal day BP was similar in the treated as compared to the untreated

Table 2.2. Characteristics of study participants.

	Normotensive	Untreated Hypertensives	Treated Hypertensives
Number	374	159	156
Age (years)	34.4±14.8	50.2±16.0 ^{***}	60.3±11.7 ^{****††}
% Female	65.2	54.7	72.4
Body mass index (kg/m ²)	26.7±7.0	30.4±7.3 ^{***}	32.9±7.7 ^{***††}
% overweight/obese	21.9/29.4	22.0/49.7 ^{***}	32.1/55.1 ^{***}
Regular tobacco intake (%)	15.0	20.8	6.4 ^{***††}
Regular alcohol intake (%)	20.9	28.3 [*]	16.7 [†]
% with DM or an HbA1c>6.1%	10.2	29.6 ^{***}	49.4 ^{****†††}
% Postmenopausal women	20.5	56.3 ^{***}	85.0 ^{****†††}
% with dyslipidaemia	19.8	22.6	28.2
% with CVD	1	0	3
% with elevated serum creatinine	1.1	1.3	4.5

DM, diabetes mellitus, HbA1c, glycated hemoglobin, CVD, cardiovascular disease. *p<0.05, **p<0.005, ***p<0.0001 vs normotensive group; †p<0.05, ††p<0.005, †††p<0.0001 vs untreated hypertensive group.

Table 2.3. Blood pressures of study participants.

	Normotensive	Untreated Hypertensives	Treated Hypertensives
Number	374	159	156
<u>Blood pressures (mm Hg)</u>			
In-office conventional SBP/DBP	116±11/77±7	150±20 ^{***} /97±10 ^{***}	142±22 ^{***†††} /88±13 ^{***†††}
24-hour SBP/DBP	112±10/69±7	130±15 ^{***} /80±11 ^{***}	123±16 ^{***†††} /75±11 ^{***†††}
Day SBP/DBP	116±10/74±8	134±15 ^{***} /86±11 ^{***}	126±16 ^{***†††} /79±11 ^{***†††}
Night SBP/DBP	104±12/61±9	123±18 ^{***} /72±13 ^{***}	118±19 ^{***††} /69±12 ^{***†}

SBP, systolic blood pressure, DBP, diastolic blood pressure. *p<0.05, **p<0.005, ***p<0.0001 vs normotensive group; †p<0.05, ††p<0.005, †††p<0.0001 vs untreated hypertensive group.

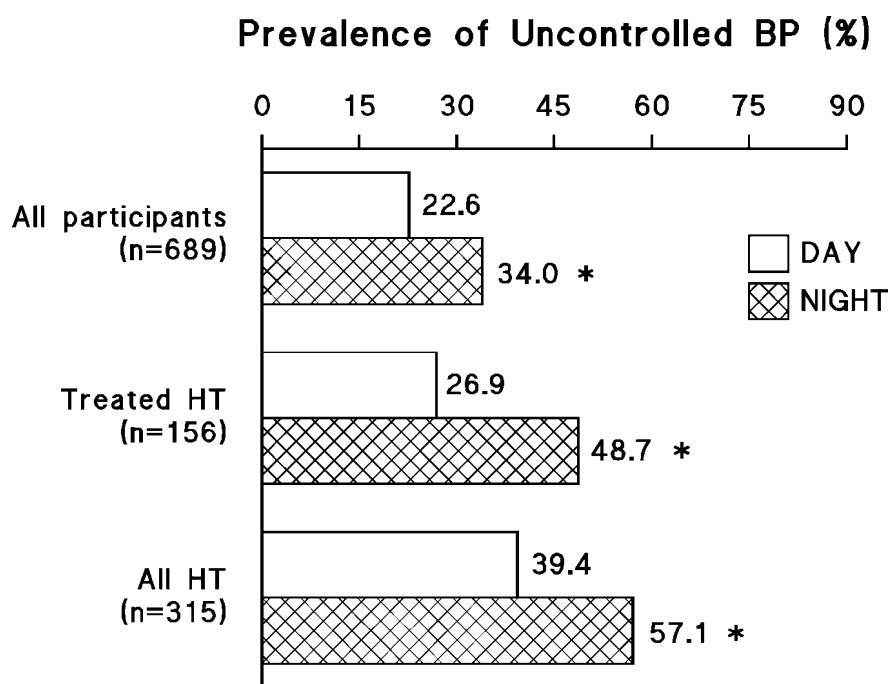


Figure 2.1. Comparison of uncontrolled day and night blood pressure (BP) values in a community sample of African ancestry. Uncontrolled day BP is considered to be $\geq 140/85$ mm Hg and uncontrolled night BP $\geq 120/70$ mm Hg as recently defined from outcome-driven thresholds (Kikuya et al 2007). * $p < 0.0001$ compared to day BP control.

Table 2.4. Comparison of uncontrolled day and night blood pressure (BP) values in various subgroups of a community sample of African ancestry.

	Prevalence of uncontrolled BP (n [%])		
	Day	Night	p value
Men (n=245)	62 (25.3)	97 (39.6)	=0.001
Women (n=444)	94 (21.2)	137 (30.9)	<0.005
Obese (n=275)	76 (27.6)	112 (40.7)	<0.005
Non-obese (n=414)	80 (19.3)	122 (29.5)	<0.001
Smokers (n=99)	36 (36.4)	42 (42.4)	=0.467
Non-smokers (n=590)	120 (20.3)	192 (32.5)	<0.0001
Systolic BP (n=689)	88 (12.8)	169 (24.5)	<0.0001
Diastolic BP (n=689)	138 (20.0)	200 (29.0)	=0.0001

Uncontrolled day BP is considered to be $\geq 140/85$ mm Hg and uncontrolled night BP $\geq 120/70$ mm Hg as recently defined from outcome-driven thresholds (Kikuya et al 2007).

hypertensives (uncontrolled night, but normal day BP: treated hypertensives = 26.9%, untreated hypertensives = 20.8%, $p = 0.23$). When using $\geq 135/85$ mm Hg as the day BP threshold, a higher prevalence of uncontrolled BP was similarly noted at night as compared to the day (% with uncontrolled BP: all participants; day = 25.4%, night = 34.0%, $p < 0.001$: treated hypertensives; day = 30.1%, night = 48.7%, $p < 0.005$: all hypertensives; day = 43.8%, night = 57.1%, $p < 0.005$).

2.3.3 Proportion of participants with white-coat or masked BP effects.

A high proportion of treated hypertensives had white-coat effects and few participants had masked hypertension (Table 2.5). The prevalence of white-coat hypertension was similar when evaluating systolic as compared to diastolic BP (Figure 2.2). As compared to the prevalence of white coat effects determined from in-office conventional BP (CBP) measurements (Table 2.5), based on home CBP measurements, a similar proportion of participants had white-coat effects (in all: $105/556=18.9\%$ and in treated hypertensives: $45/135=33.3\%$). The proportions of participants with white-coat or masked hypertensive effects was similar in men and women, obese or non-obese, and in smokers and in non-smokers (data not shown).

2.3.4 Factors associated with white-coat effects.

Including age, sex, treatment for hypertension, educational level, and level of employment in a multivariate model, both an older age (odds ratio=1.03, confidence interval=1.02-1.05, $p < 0.0001$) and treatment for hypertension (odds ratio=2.11 confidence interval=1.25-3.55, $p < 0.005$) were independently associated with white-coat effects. The majority of participants with white-coat effects had in-office CBP values that

Table 2.5. Proportion of participants who were normotensive (NT), had white coat effects, had masked hypertensive effects or had sustained increases in conventional and day blood pressure (BP) (hypertensives-HT).

	Sample number (%)			
	NT	White coat	Masked	HT
All participants(n=689)	390 (56.6)	124 (18.0)	43 (6.2)	132 (19.2)
All hypertensives (n=315)	53 (16.8)	124 (39.4)	6 (1.9)	132 (41.9)
Treated hypertensives (n=156)	53 (34.0)	56 (35.9)	6 (3.8)	41 (26.3)

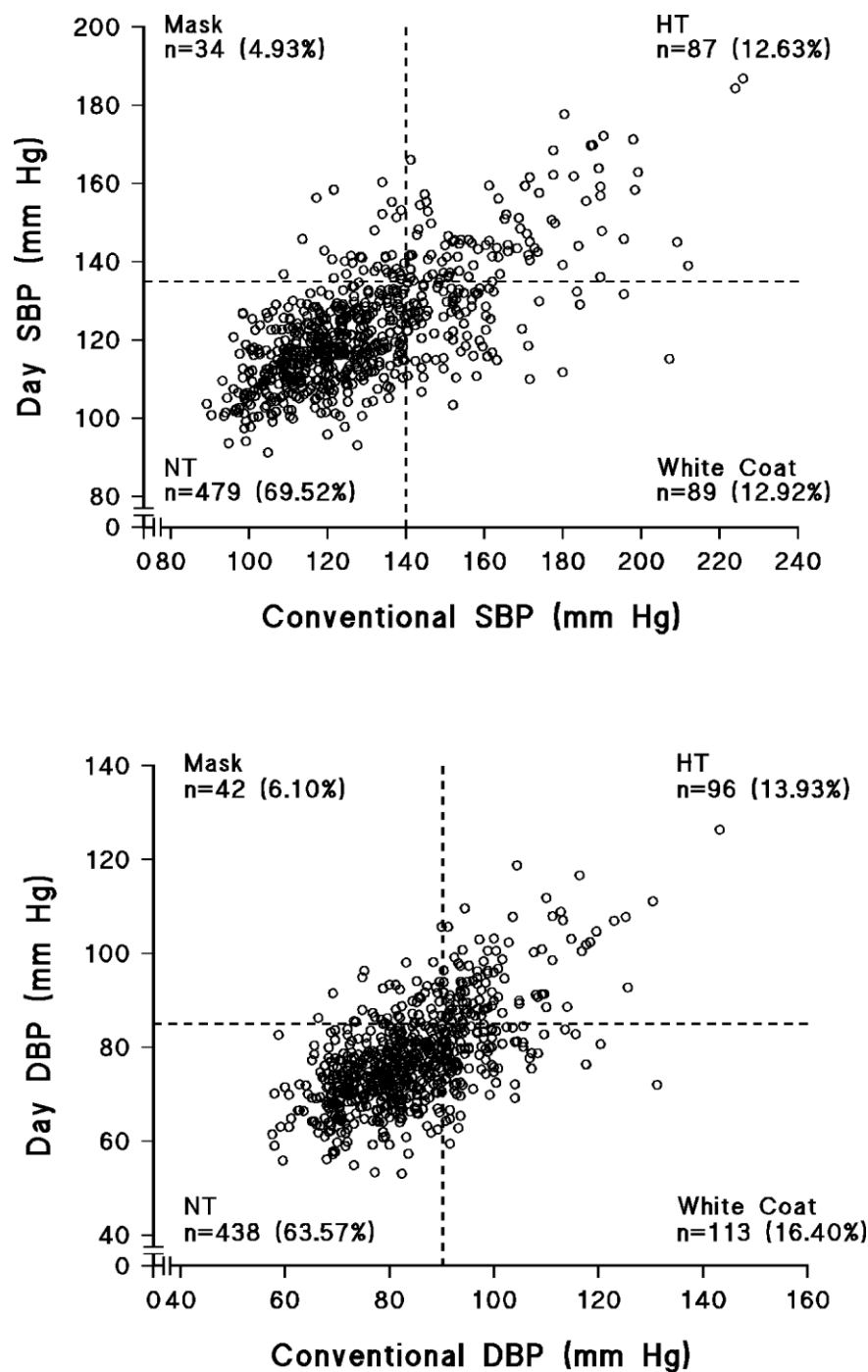


Figure 2..2 Relationship between conventional (conv.) and day ambulatory blood pressures (BP) for either systole (SBPconv. or Day SBP) or diastole (DBPconv. or Day DBP) showing the proportion of participants with either normal or increased conventional or day SBP or DBP values. The dashed lines represent current conventional and day BP thresholds. The day BP thresholds are derived from recently defined outcome-driven thresholds (Kikuya et al 2007). NT, normotensive; HT, hypertensive; Mask, masked hypertensives; White coat, white coat hypertensives.

were <160/100 mm Hg (grade 1 hypertension). In this regard, in participants with white coat effects, 75% of all hypertensives (n=93/124), 71% of treated hypertensives (n=40/56) and 77.9 % of untreated hypertensives (n=53/68) had grade I hypertension.

2.3.5 Conventional versus ambulatory BP control.

Irrespective of whether assessed in all participants, treated hypertensives, or all hypertensives, the proportion of participants with an uncontrolled CBP was higher than that of participants with an uncontrolled 24-hour BP (Figure 2.3, upper panel). These differences were noted whether or not CBP was determined using in-office or home (data not shown) BP measurements. Differences in CBP and 24-hour BP control rates were noted in men and women, obese or non-obese, and in non-smokers (Table 2.6). Similar differences in CBP and ABP control rates were noted for both systolic and diastolic BP (Uncontrolled systolic CBP=25.5%, ABP=17.9%, $p<0.005$; uncontrolled diastolic CBP=30.3%, ABP=19.2%, $p<0.0001$). Differences in uncontrolled CBP and ABP were abolished when data from participants with white-coat effects were censored (Figure 2.3, lower panel).

2.4 Discussion

The main findings of the present study are that in a randomly selected community sample of African ancestry, although night was worse than day BP control, the high proportion of participants with white-coat effects translated into a marked underestimation of BP control at a community level, when CBP was employed to define BP control. In hypertensives the prevalence of an uncontrolled 24-hour BP was

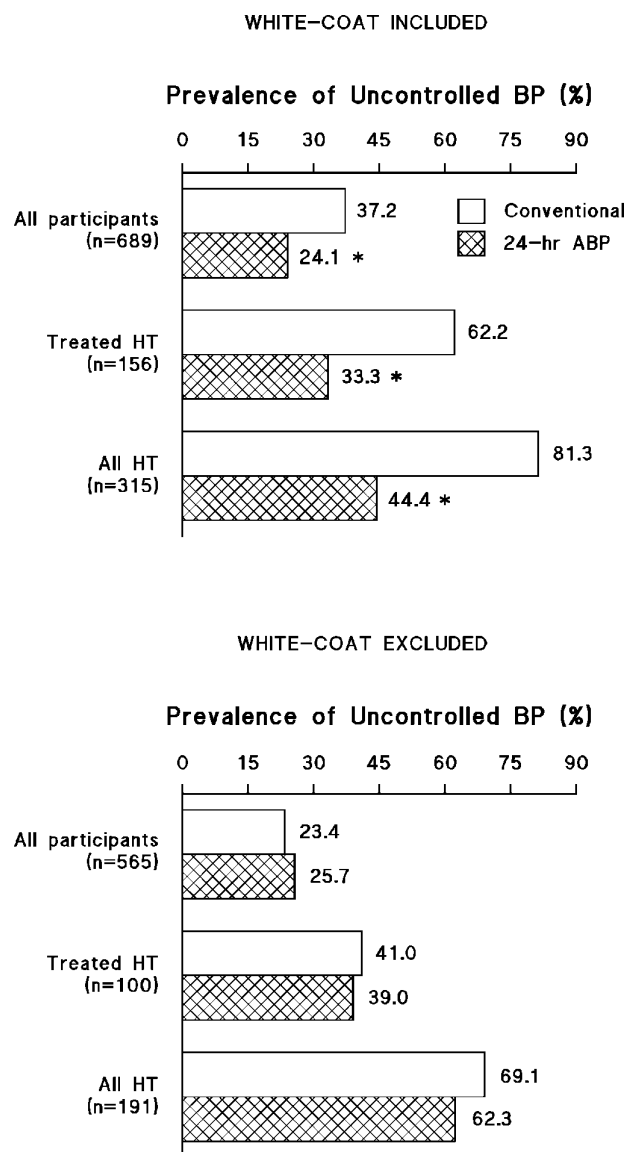


Figure 2.3. Comparison of the proportion of participants with an uncontrolled conventional (CBP) and uncontrolled 24-hour ambulatory (24-hr ABP) blood pressure (BP) in a community sample of African ancestry. The upper panel shows data in all participants. The lower panel shows data after censoring participants with white coat-effects. Uncontrolled conventional BP is considered to be $\geq 140/90$ mm Hg and uncontrolled 24-hr ABP $\geq 130/80$ mm Hg as recently defined from outcome-driven thresholds (Kikuya et al 2007). * $p < 0.0001$ compared to CBP control.

Table 2.6. Proportion of participants with uncontrolled conventional (CBP) as compared to uncontrolled 24-hour ambulatory (24-hr ABP) blood pressure (BP) in important subgroups of the study sample.

	Number (%) with uncontrolled		p-value*
	CBP (in-office)	24-hr ABP	
Women (n=444)	156 (35.1)	99 (22.3)	<0.0001
Men (n=245)	100 (40.8)	67 (27.4)	<0.005
Obese (n=275)	133 (48.4)	82 (29.8)	<0.0001
Non-obese (n=414)	123 (29.7)	84 (20.3)	<0.005
Smokers (n=99)	40 (40.4)	31 (31.3)	=0.24
Non-smokers (n=590)	216 (36.6)	135 (22.9)	<0.0001

*For comparison of proportion of participants with uncontrolled CBP versus uncontrolled 24-hour ABP.

approximately half that of the prevalence of an uncontrolled CBP, whilst after censoring data from participants with white coat effects, CBP and ABP control rates were the same.

Although groups of African ancestry have been reported to have a considerably worse BP control than other ethnic groups (Hertz et al 2005, Cutler et al 2008, Steyn et al 2008), these control rates have been estimated from CBP measurements. As thresholds for ABP control account for lower ABP values as compared to CBP values (Kikuya et al 2007), in surveillance studies one may expect CBP control rates to closely reflect ABP control rates. In contrast however, the present study suggests that irrespective of whether CBP is measured in the office or in the home, because of a high prevalence of white-coat effects, CBP measurements in this ethnic group may considerably overestimate prevalence rates of an uncontrolled BP.

An overestimation of the prevalence of uncontrolled ABP when employing CBP measurements was particularly striking in hypertensives in whom 81.3% had an uncontrolled CBP, whilst 44.4% had an uncontrolled 24-hour ABP. Extrapolating these figures to previous estimates of uncontrolled BP in groups of black African descent in South Africa (Steyn et al 2001), the previously reported age-adjusted figure of 85-93% of uncontrolled BP in all hypertensives in this group may require downward adjustments to 46-51%. This value is better than the age-adjusted prevalence of uncontrolled BP of 67% in all hypertensives of this ethnic group (Cutler et al 2008) and in other ethnic groups (Hertz et al 2005, Cutler et al 2008, Lloyd-Jones et al 2005); in the United States and the prevalence rates of uncontrolled BP in all hypertensives in England (62%) and Italy (67%) in 1998 (Wolf-Maier et al 2004). Therefore, the present study highlights the need for surveillance studies to adjust for estimated prevalence rates of white-coat effects.

In contrast to the 10.5% of Caucasian and Japanese participants from four population samples reported to have white-coat hypertension (Hansen et al 2007), in the present study using the same thresholds as this previous study (Hansen et al 2007), 18.0-18.5% of participants had white-coat effects. Neither education level, nor current level of occupation could account for excessive white coat effects. The majority (71%) of participants with white-coat effects had grade I hypertension, and an older age and antihypertensive treatment were independently associated with white-coat effects. An equivalent proportion of participants with treated (35.9%)(who were also aware of their condition) and untreated (42.8%)(not previously diagnosed) hypertension had white-coat effects, suggesting that this effect is an alerting response either to the presence of the nurse or to the BP measurement *per se* and not to an awareness of the condition. I cannot attribute the white-coat response to the in-office environment as similar results were obtained with home as compared to in-office BP values.

The higher prevalence of uncontrolled night as compared to day BP in the present study is consistent with an attenuated decline in BP at night and the higher night for a given day BP value noted in groups of African as compared to European ancestry (Wang et al 2006, Profant and Dimsdale 1999). However, alternative explanations include an inability of thiazide diuretic monotherapy, which the majority of treated hypertensives (60.0%) were receiving, to provide appropriate nocturnal BP control and that all antihypertensives were taken in the morning, thus providing better day as compared to night BP cover. Nevertheless, a similar proportion of treated (26.9%) and untreated (20.8%) hypertensives had an uncontrolled night and controlled day BP. Given the high prevalence of obesity in the community studied, one potential mechanism responsible for a predisposition to higher night BP values is sleep apnoea. However, differences in day and night control rates were noted in both obese and non-obese participants and hence the role of obesity, and by inference sleep apnoea, may not be

that important. Irrespective of the mechanisms responsible for the higher prevalence of uncontrolled night as compared to day BP in the present study, current evidence suggests that 24-hour ABP is more important than either day or night BP considered separately (Boggia et al 2007).

At a population level white-coat hypertension has been demonstrated to carry a risk for cardiovascular events that is similar to normotensives (Hansen et al 2007). It is possible therefore that in urban, developing communities of African descent, CBP measurements may result in the treatment of, up-titration of the dose of therapy in, or the addition of further therapy in a significant number of people who are not at risk for the adverse effects of BP because they have white-coat effects. It is possible that these potentially inappropriate actions may occur in 16.9% of the community, with obvious major cost implications to the health care system. Nevertheless, of the participants who I have identified as being at risk of receiving inappropriate therapy, a significant portion of these may require additional therapy to achieve lower BP targets because of their global risk profiles (the community has a high prevalence of diabetes mellitus or an HbA1c>6.1%). However, in these cases I also assume that ABP targets should be proportionately lower. Furthermore, as white-coat hypertension is associated with a lack of nocturnal BP dipping (Bochud et al 2009), a recognised risk factor for cardiovascular damage, it is possible that a proportion of participants with white-coat effects in the present study may ultimately develop cardiovascular damage and hence may benefit from antihypertensive therapy. Moreover, as argued in chapter 3, whether the alerting response across the full adult BP spectrum reflects a pathological state has not been fully elucidated. Further studies, such as that described in chapter 3, are required to answer this question.

The limitations of the present study are as follows: Although I could show similar results in a number of relevant subgroups, I compared CBP and ABP control rates in one

community of African ancestry. As this was a typically urban, previously disadvantaged, economically developing community, further studies are required to evaluate whether a similar high prevalence of white-coat effects characterise rural communities or economically developed communities of African ancestry. Second, although ABP has been demonstrated to be a stronger predictor of cardiovascular outcomes than CBP in a number of populations (Ohkubo et al 2005, Kikuya et al 2005, Hansen et al 2005, Bjorklund et al 2003, Hansen et al 2007) it is possible that this may not be the case in the present study sample. Indeed, as demonstrated in chapter 3, it is possible that the alerting response represents a pathological state.

In conclusion, the present study indicates that in a community sample with a high prevalence of white-coat effects, CBP measurement may considerably overestimate the risk related to uncontrolled ABP. Therefore, to provide a more accurate assessment of the cardiovascular risk associated with BP in surveillance studies, it may be necessary to adjust CBP control rates for the prevalence of white-coat effects. Further, to avoid a considerable proportion of people of African ancestry receiving unnecessary antihypertensive medication, cost-effective strategies for the identification of white-coat effects may be necessary. However, this should only be a consideration once it is established that alerting responses in the present community represent a truly benign state that does not respond to BP lowering therapy.

CHAPTER 3

**“White-Coat” Effects Account for a Significant Proportion of
Nurse-Derived Blood Pressure-Target Organ Relations.**

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Abstract

Although, there is significant evidence to support the notion that ambulatory is superior to in-office blood pressure (BP) in predicting cardiovascular outcomes, nurse-derived BP measurements are often as closely associated with organ damage as out-of-office ambulatory BP. However, the extent to which relationships between nurse-derived BP measurements and organ damage reflect a white-coat effect (isolated increase in in-office BP) as opposed to the adverse effects of BP *per se* are unknown. In 750 participants from a community sample I determined the extent to which relationships between nurse-derived blood pressures (BP) and cardiovascular damage may be attributed to isolated increases in in-office systolic BP (SBP) independent of ambulatory BP. Target organ changes were determined from carotid-femoral pulse wave velocity (PWV) (applanation tonometry and SphygmoCor software) (n=662) and left ventricular mass indexed to height^{2.7} (LVMI) (echocardiography)(n=463). Nurse-derived office BP was associated with organ changes independent of 24-hour BP (LVMI; partial $r=0.15$, $p<0.005$, PWV; partial $r=0.21$, $p<0.0001$) and day BP. However, in both unadjusted ($p<0.0001$ for both) and multivariate adjusted models (including adjustments for 24-hour BP)(LVMI; partial $r=0.14$, $p<0.01$, PWV; partial $r=0.21$, $p<0.0001$) nurse office-day SBP (an index of isolated increases in in-office BP) was associated with target organ changes independent of ambulatory BP and additional confounders, with the highest quartile (≥ 15 mm Hg) showing the most marked increases in LVMI ($p<0.0005$) and PWV ($p<0.0001$) as compared to the lowest quartile (< -5 mm Hg). These relationships were reproduced in those with normotensive day BP values and the quantitative effect of nurse office-day BP on target organ changes was at least equivalent to that of ambulatory BP. In conclusions, nurse-elicited white-coat effects are associated with a significant proportion of the relationship between nurse-derived BP and target organ changes independent of

ambulatory BP. Therefore, high quality nurse-derived BP measurements do not approximate the impact of BP effects *per se* on cardiovascular damage.

3.1 Introduction

There is significant evidence to support the notion that ambulatory is superior to in-office blood pressure (BP) in predicting cardiovascular outcomes (Perloff et al, 1983, 1989, Ohkubo et al 1994, Imai et al 1996, Redon et al 1998, Khattar et al 1999, Verdecchia et al, 1994, 1998, 2002, Staessen et al 1999, Robinson et al 2001, Clement et al 2003, Kikuya et al 2005, Dolan et al 2005, Fagard et al 2004, 2008, Hansen et al 2005, Ingelsson et al 2006, Dawes et al 2006, Schwartz et al 2007, Astrup et al 2007, Eguchi et al 2008, Palmas et al 2009, Dzrelinska et al 2009, Mesquita-Bastos et al 2010, Boggia et al 2011). These effects have been attributed in-part to isolated increases in in-office BP (increased in-office compared to day BP often called white-coat effects or alerting responses). In this regard, meta-analyses (Hansen et al 2007, Fagard et al 2007) have demonstrated that an increased in-office, but normal out-of-office BP predicts cardiovascular outcomes to a similar extent as that of sustained normotension (normal in and out-of-office BP) and some studies have failed to demonstrate a relationship between isolated increases in in-office BP and organ damage (White et al 1998, Verdecchia et al 1992, Grosse et al 1993). Although alternative studies suggest a pathological role for isolated increases in in-office BP (Verdecchia et al 2005, Mancia et al 2006, Kuwajima et al 1993, Glen et al 1996, Palatini et al 1997, Muscholl et al 1998, Owens et al 1998, Palatini et al 1998, Landray et al 1999, O'Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Segal et al 2001); decreases in the difference between office and day BP (an index of isolated increases in in-office BP) produced by antihypertensive therapy are unrelated to improvements in organ damage (Fagard et al 2000, Paratti et al 2000). Hence, although it is still unclear as to whether

isolated increases in in-office BP contribute to risk prediction, it may be desirable to exclude these differences when implementing BP-lowering therapy as these differences do not reflect the impact of BP on cardiovascular damage. In this regard, it is possible that nurse-recorded in-office BP values may better reflect the adverse effects of BP on cardiovascular damage.

Although nurses measure in-office BP values that are higher than out-of-office values, the difference is nevertheless less evident than that of physicians (Little et al 2002). This limited effect on in-office increases in BP of nurse-derived BP measurements may explain why nurse-derived values are often as closely associated with organ damage as out-of-office ambulatory BP (Nystrom et al 2005, Veerman et al 1996, de Blok et al 1991, Jula et al 1999, Moran et al 2006, Woodiwiss et al 2009). However, the extent to which relationships between nurse-derived BP measurements and organ damage reflect an isolated increase in in-office BP as opposed to the adverse effects of BP *per se* are unknown. In the present study I therefore evaluated the extent to which nurse-derived BP measurements may induce an increase in in-office as compared to day BP that is related to target organ changes independent of ambulatory BP and additional confounders.

3.2 Methods

3.2.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The

present study is an extension of the study described in chapter 2 and reflects data obtained by end 2011. As such the study design has largely been described in chapter 2 (section 2.2.1). Of the 700 households approached up until end 2011, nuclear families from 397 households agreed to participate (56.7%). Of the 1191 participants recruited by end 2011, 750 participants had 24-hour ambulatory BP monitoring that met with the European Society of Hypertension (ESH) guidelines (longer than 14 and 7 readings for the computation of day and night means, respectively) (O'Brien et al 2003). Of these participants 662 had carotid-femoral (aortic) pulse wave velocity (PWV), and 463 had echocardiography.

3.2.2 Clinical, demographic and anthropometric measurements.

A standardized questionnaire was administered to obtain demographic and clinical data as described in chapter 2 (section 2.2.2). Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was $\geq 25 \text{ kg/m}^2$ and obese if their BMI was $\geq 30 \text{ kg/m}^2$. Blood tests of renal function, liver function, blood glucose, haematological parameters, and percentage glycated haemoglobin ($\text{HbA}_{1\text{C}}$) (Roche Diagnostics, Mannheim, Germany) were performed. Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an $\text{HbA}_{1\text{C}}$ value greater than 6.1% (see section 2.2.2).

3.2.3 Blood pressure.

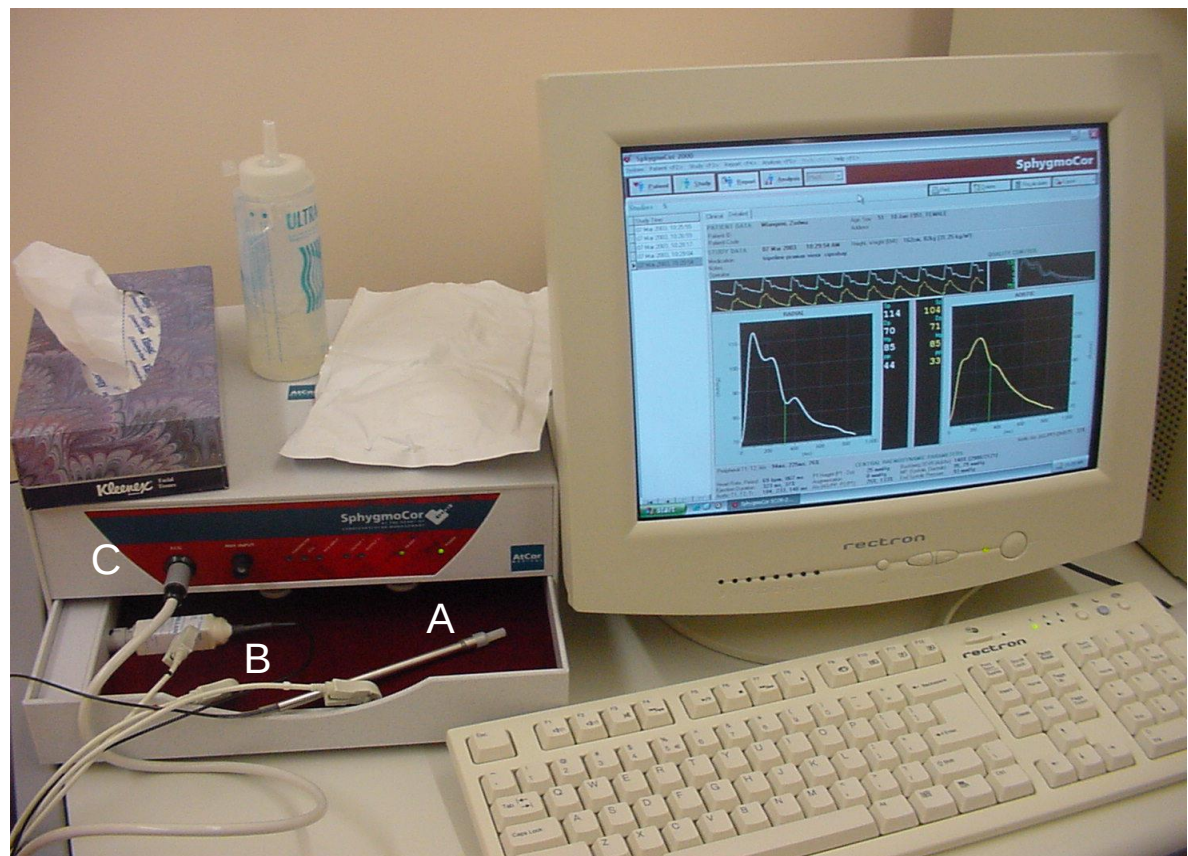
High quality conventional BP measurements were obtained by one trained nurse according to guidelines using a standard mercury sphygmomanometer as described in

chapter 2 (section 2.2.3). In the present study sample the frequency of identical consecutive recordings was 0.14% for systolic BP and 1.63% for diastolic BP. No BP values were recorded as an odd number. Of the systolic and diastolic BP readings, 30.4% ended on a zero (expected=20%). Hypertension was defined as CBP $\geq$ 140/90 mm Hg or the use of antihypertensive medication. Ambulatory 24-hour, day and night BP were determined using SpaceLabs monitors (model 90207) as described in chapter 2 (section 2.2.3). The average ($\pm$ SD) number of BP recordings obtained was 61.6 ± 11.2 (range=25 to 81) for the 24-hour period, 28.9 ± 6.6 (range=25 to 81) for the day and 9.5 ± 0.8 (range=7 to 11) for the night periods. A normal day BP was considered as $<135/85$ mm Hg.

3.2.4 Measures of target organ changes

3.2.4.1 Pulse wave velocity.

Aortic stiffness was estimated using carotid-femoral (aortic) pulse wave velocity (PWV). Carotid-femoral PWV has been demonstrated in a number of studies to predict cardiovascular outcomes independent of traditional risk factors including CBP (O'Rourke et al 2002). Carotid-femoral PWV was determined using applanation tonometry and SphygmoCor software as previously described (Shiburi et al 2006, Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010). After participants had rested for 15 minutes in the supine position, arterial waveforms at the carotid and femoral artery pulses were recorded by applanation tonometry, each during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) (Norton et al 2012, Shiburi et al 2006) (Figure 3.1). Recordings where the systolic or diastolic variability of consecutive



- A Applanation tonometer.
- B Electrocardiograph electrodes.
- C SphygmoCor device.

Figure 3.1 SphygmoCor device coupled to an applanation tonometer used to determine aortic pulse wave velocity.

waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. Aortic PWV was measured from sequential waveform measurements at carotid and femoral sites as previously described (Shiburi et al 2006) (Figure 3.2). Pulse wave transit time i.e. the time it takes the pulse wave to travel from the carotid to the femoral site, was determined as the difference between the times taken to generate the femoral and carotid pulse waveforms. To assess the differences in time of the generation of the femoral and carotid pulse waveforms, a single lead electrocardiogram was performed concurrently with pulse waveform sampling. The time delay in the pulse waves between the carotid and femoral sites was determined using the R wave as a fiducial point. Pulse transit time was taken as the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. Aortic PWV was calculated as distance (meters) divided by transit time (seconds). An increased PWV was identified as a PWV > 10 m/sec (Van Bortel et al 2012).

3.2.4.2 Echocardiography.

Echocardiographic measurements were performed using previously described methods on the same echocardiogram (HP-5500, Palo Alto, Ca) (Norton et al 2008, Woodiwiss et al 2008, Libhaber et al 2008, Woodiwiss et al 2009). All measurements were recorded and analyzed by two experienced investigators (CL and AJW) who were unaware of the clinical data of the participants. All participants were assessed for mitral valve abnormalities as determined using 2-dimensional and color Doppler imaging. Left ventricular (LV) dimensions were determined using two-dimensional directed M- mode echocardiography in the short axis view and these recordings analyzed according

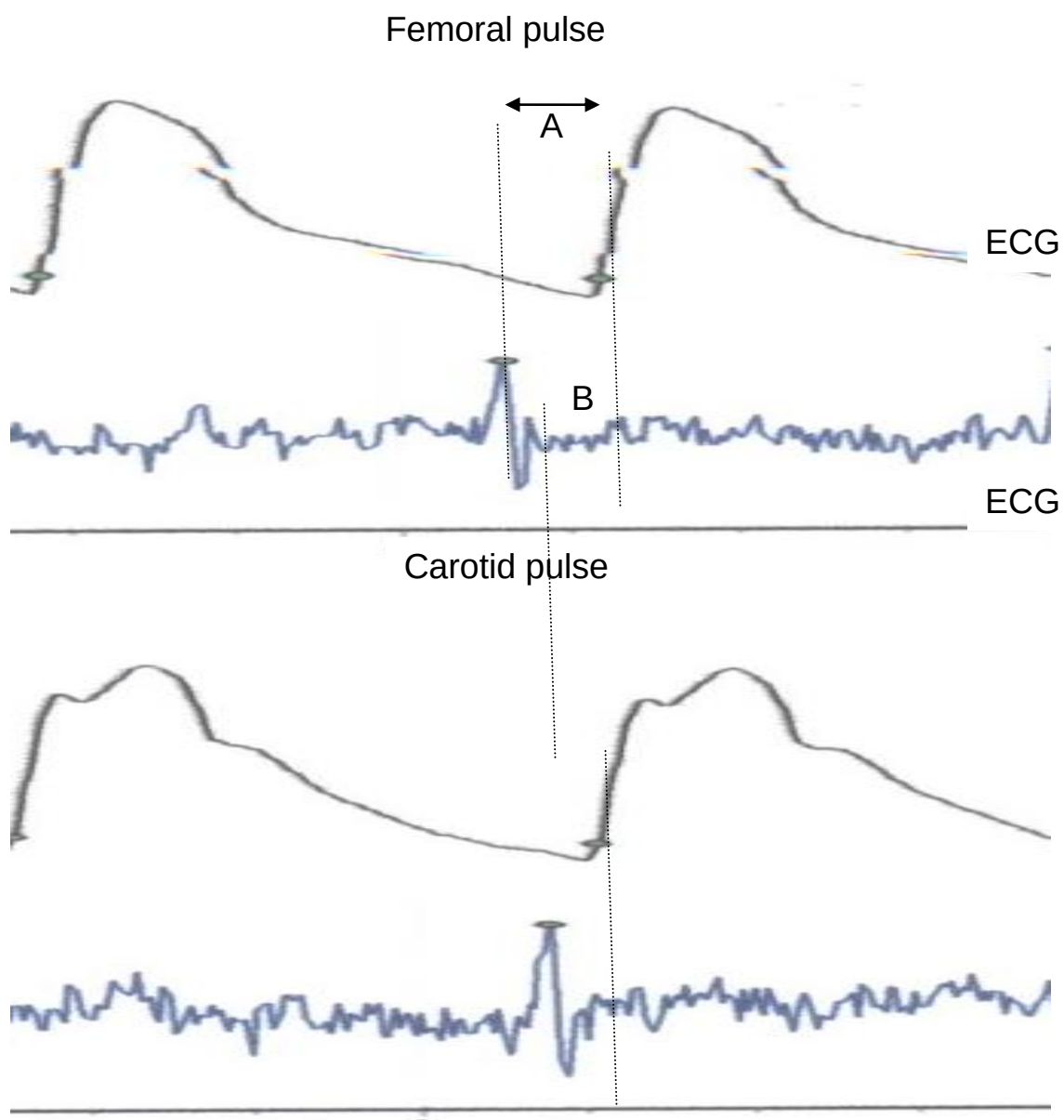


Figure 3.2. Examples of femoral and carotid artery pulse waves obtained using applanation tonometry from the same participants. Together with simultaneous electrocardiographic (ECG) recordings aortic pulse wave velocity (PWV) is calculated. The arrows indicate the time between electrical events and the arterial pressure changes in the carotid and femoral arteries used to calculate PWV. See text for a further description.

to the American Society of Echocardiography convention (Sahn et al 1978). During recordings, the transducer was placed perpendicular to the chest wall or pointed slightly inferiorly and laterally at the end of the long axis. M-mode images were obtained perpendicular to the posterior wall and as close to the mitral leaflet as possible without images of the mitral leaflet appearing. The interventricular septal wall thickness (IVS) at end diastole and end systole, the posterior wall thickness (PWT) at end diastole and end systole and the end diastolic and end systolic internal dimensions of the left ventricle were measured only when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surfaces of both the septal and posterior wall were clearly visible. Figure 3.3 shows a representative M-mode image employed to assess left ventricular mass. Left ventricular (LVM) mass was derived according to an anatomically validated formula (Devereux et al 1986) ($LVM = 0.8 \times [1.04 (LVEDD + IVS + PWT)^3 - (LVEDD)^3] + 0.6g$) and indexed to height^{2.7} (LVM index, LVMI). Left ventricular hypertrophy (LVH) was defined as a LVMI >51 g/m^{2.7} for both women and men (Nunez et al 2005).

Intra-observer variability studies were conducted on 29 subjects on whom repeat echocardiographic measurements have been performed within a two week period of the initial measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness and posterior wall thickness were 0.76, 0.94 and 0.89 (all $p < 0.0001$) respectively, and the variances (mean % difference $\pm$ SD) were $0.12 \pm 5.95\%$, $0.77 \pm 4.47\%$ and $0.67 \pm 5.57\%$ respectively. In addition, no significant differences between repeat measurements were evident on paired t-test analysis ($p = 0.99$, $p = 0.42$ and $p = 0.48$ respectively). Inter-observer variability studies were conducted on 26 participants on whom the two echocardiographers involved in obtaining measurements performed echocardiography on the same participants whilst blinded to each others measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness

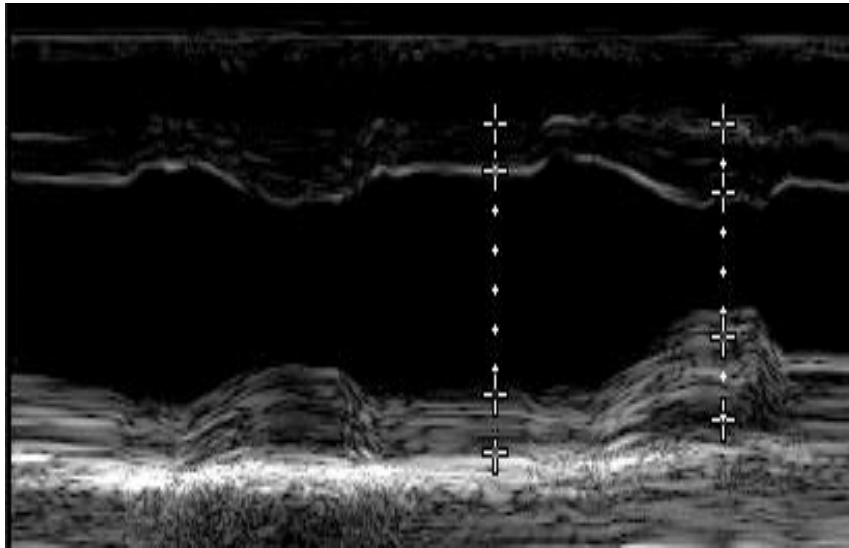


Figure 3.3. A two-dimensional guided M-mode echocardiographic image derived from a Hewlett Packard model 5500 utilised to assess left ventricular dimensions.

and posterior wall thickness were 0.96, 0.84 and 0.88 (all $p < 0.0001$) respectively, and the variances (mean % difference $\pm$ SD) were $0.49 \pm 2.71\%$, $-1.69 \pm 7.19\%$ and $0.23 \pm 5.89\%$ respectively. In addition, no significant differences between measurements were evident on unpaired t-test analysis ($p = 0.38$, $p = 0.26$ and $p = 0.85$ respectively).

3.2.5 Data analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Data are shown as mean $\pm$ SD or mean $\pm$ SEM. Means and proportions were compared by the large-sample z-test and the χ^2 -statistic, respectively. Relationships were determined using multivariate (continuous data) or logistic (categorical data) regression analysis with appropriate confounders included in each model. Adjustments were made for the impact of day, night, or 24-hour BP, age, sex, body weight (for LVMI) or BMI (for PWV), the presence of diabetes mellitus or an HbA1c $> 6.1\%$, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake. When assessing relationships with PWV, office mean arterial pressure (distending pressure) was also included as an adjustor. The linear relationship between MAP and PWV ($r = 0.47$, $p < 0.0001$) was equally as strong as the exponential relationship between MAP and PWV ($r = 0.46$, $p < 0.0001$). To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To ensure that nurse-elicited white-coat effects were independently associated with target organ changes irrespective of absolute BP, sensitivity analysis was conducted in those with a normotensive day BP and in hypertensives separately. As in a multivariate model, age and treatment for hypertension

were correlated with nurse office-day BP, and age and treatment for hypertension were correlated with each other, BMI and diabetes mellitus or an HbA1c>6.1%; to ensure that multiple colinearity did not influence the results, sensitivity analysis was also conducted in participants not receiving antihypertensive treatment and without age in the regression model.

3.3 Results

3.3.1 General characteristics of participants.

Table 3.1 gives the characteristics of the study group. In general, more women than men participated. A high proportion of participants were obese or had hypertension or diabetes mellitus/HbA1c>6.1%. Of the group 20% had LV hypertrophy as defined by a LVMI>51 g/m^{2.7} and 7% an increased aortic PWV as defined by a value >10 m/sec. The demographic and clinical characteristics of those with and without ambulatory BP measurements that met with prespecified quality control criteria are shown in Table 3.2. As it was more frequently difficult to obtain high quality ambulatory 24 hour BP recordings in obese participants, those without 24-hour measurements that met with prespecified quality control criteria were more obese and these participants had a trend for a higher systolic BP (SBP). Nurse recorded SBP and diastolic (DBP) BP values were higher than day SBP and DBP values. Day SBP and DBP values were higher than night BP values. Nurse recorded in-office pulse rate was lower than day pulse rate.

Table 3.1. Demographic, anthropometric, clinical and haemodynamic characteristics of study sample.

	All (n=750)	Echo (n=464)	Pulse wave (n=662)
% Female	63.9	63.2	62.7
Age (years)	43.5±18.0	43.0±17.9	43.3±18.3
Body mass index (kg/m ²)	28.8±7.6	28.7±7.4	28.1±7.0
% Overweight/obese	25.1/38.9	25.7/39.2	25.4/36.3
Waist circumference (cm)	89.2±15.9	89.3±16.2	88.1±15.3
Regular tobacco intake (%)	14.8	13.8	15.7
Regular alcohol intake (%)	21.2	19.0	21.6
% with DM or an HbA _{1c} >6.1%	25.2	24.6	24.6
Total/HDL cholesterol	3.54±1.31	3.58±1.30	3.52±1.30
% Hypertensive	45.1	45.3	44.0
% Treated for hypertension	22.9	23.3	22.7
Nurse office SBP/DBP (mm Hg)	128±21/84±12	128±21/84±12	128±22/83±12
Mean arterial BP (mm Hg)	98.9±14.5	98.7±14.6	98.5±14.6
Pulse rate (beats/min)	70±11	70±10	70±11
24-Hour SBP/DBP (mm Hg)	118±15/73±10	119±15/73±10	118±15/73±10
Day SBP/DBP (mm Hg)	123±15/78±10	123±15/78±11	122±15/77±10
Night SBP/DBP (mm Hg)	111±17/65±12	112±17/65±12	111±17/65±12
Nurse office-day SBP* (mm Hg)	5.8±15.4	4.8±14.8	5.6±15.6
Nurse office-day DBP* (mm Hg)	6.3±9.8	5.8±9.7	6.0±9.7
Nurse office-day pulse rate (beats/min)	-13.1±11.9	-12.6±11.9	-13.1±11.8
% Isolated office hypertension	18.0	15.1	17.2
Left ventricular mass index (LVMI) (g/m ^{2.7})	-	43.0±14.3	-
% with LVMI>51 g/m ^{2.7}	-	20.0	-
Aortic pulse wave velocity (m/sec)	-	-	6.47±2.75
% with pulse wave velocity>10 m/sec	-	-	7.10

Echo, echocardiography; DM, diabetes mellitus; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Index of isolated increases in in-office BP.

Table 3.2. Demographic, anthropometric, clinical and haemodynamic characteristics of those with or without ambulatory blood pressure (ABP) data that met with European Society of Hypertension guidelines for quality control criteria.

	With (n=750)	Without (n=441)	p-value
% Female	63.9	67.6	=0.21
Age (years)	43.5±18.0	43.6±18.4	=0.93
Body mass index (kg/m ²)	28.8±7.6	30.7±8.7	=0.0001
% Overweight/obese	25.1/38.9	19.5/49.2	<0.05/<0.001
Waist circumference (cm)	89.2±15.9	92.1±17.7	<0.005
Regular tobacco intake (%)	14.8	15.2	=0.87
Regular alcohol intake (%)	21.2	21.1	=1.0
% with DM or an HbA _{1c} >6.1%	25.2	25.4	=0.95
Total/HDL cholesterol	3.52±1.32	3.62±2.65	=0.46
% Hypertensive	45.1	45.1	=1.0
% Treated for hypertension	22.9	25.6	=0.29
Nurse office SBP/DBP (mm Hg)	128±21/84±12	131±24/85±14	<0.05/0.21

DM, diabetes mellitus; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure.

3.3.2 Does nurse office minus day BP represent an alerting response?

On bivariate analysis, nurse office-day SBP was directly related to nurse office SBP (data not shown) and nurse office-day pulse rate (Figure 3.4), but not day SBP (Figure 3.4). These relationships or the lack thereof were noted in both those with a normotensive day BP and hypertensives (data not shown). Ambulatory BP did not increase across quartiles of nurse office-day BP (data not shown).

3.3.3 Nurse office BP is associated with target organ changes independent of day or 24-hour BP.

The multivariate adjusted relationships between 24-hour SBP and LVMI (partial $r=0.14$, confidence intervals= $0.05-0.23$, $p<0.005$) or PWV (partial $r=0.14$, confidence intervals= $0.07-0.22$, $p<0.0005$) were similar to those between nurse office SBP and target organ changes (see Figure 3.5 for partial r values and confidence intervals, $p>0.09$ for comparison of partial r values using Z statistics). In the same multivariate models, nurse office SBP was associated with target organ changes independent of day or 24-hour SBP (Figure 3.5).

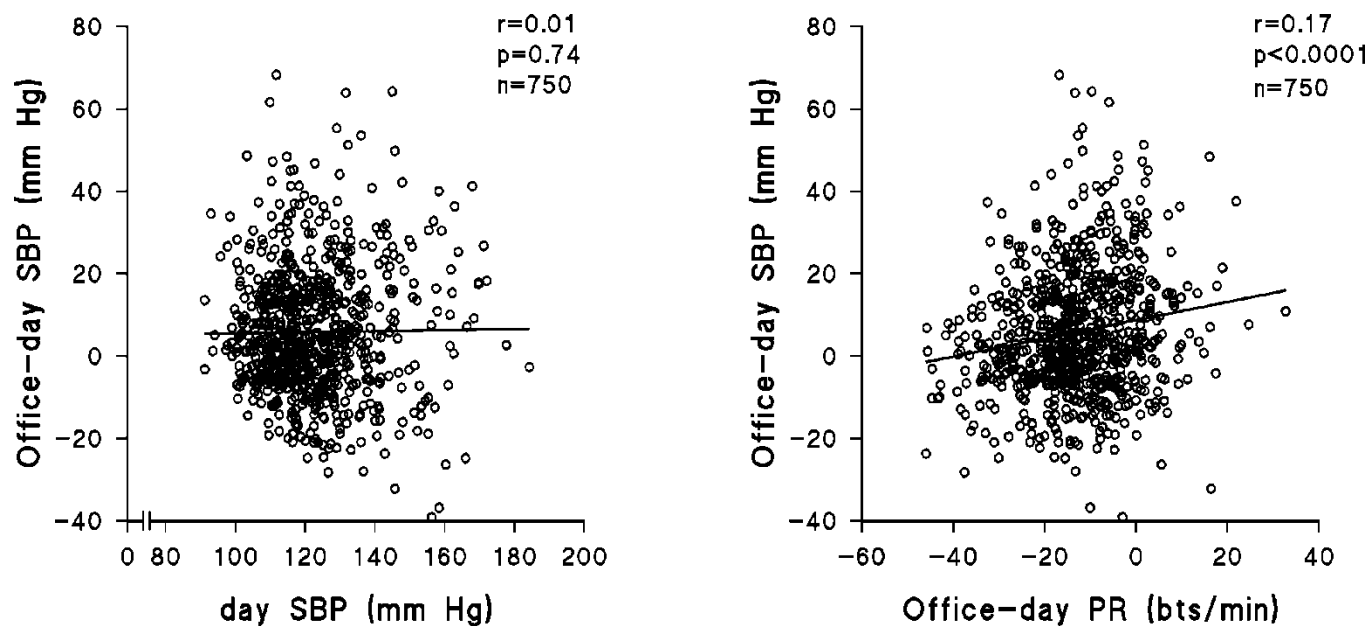


Figure 3.4. Relationships between nurse-derived office systolic blood pressure (SBP) minus ambulatory day SBP (isolated increases in in-office SBP with nurse measurement) and ambulatory day SBP or office minus day pulse rate (PR).

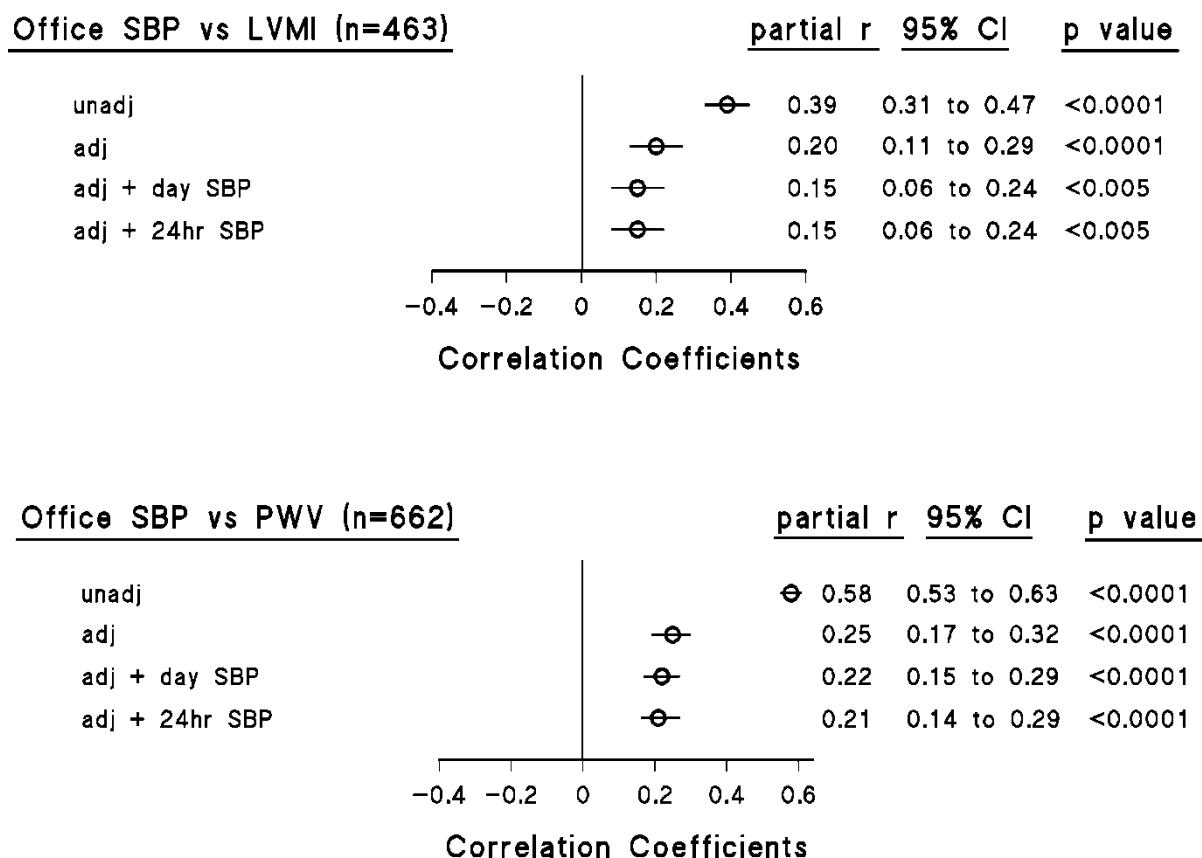


Figure 3.5. Independent relationships between nurse-derived office systolic blood pressure (SBP) and target organ changes before and after adjustment for day and 24-hour (24hr) SBP. LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension, regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). †Further adjusted for non-independence of family members.

3.3.4 Relationship between nurse office-day BP and target organ changes.

On bivariate and multivariate adjusted analyses, nurse office-day SBP was directly related with both LVMI and PWV independent of either day or 24-hour SBP and additional confounders (Table 3.3). These relationships were noted in sensitivity analysis conducted in those with a normotensive day BP and hypertensive participants separately (Table 3.2) and in those not receiving treatment for hypertension and without age as an adjustor (With 24-hour SBP as an adjustor: Nurse office-day SBP vs LVMI, partial $r=0.20$, confidence intervals=0.10-0.30, $p<0.0005$; Nurse office-day SBP vs PWV, partial $r=0.31$, confidence intervals=0.23-0.39, $p<0.0001$). No interaction between nurse office-day SBP and day SBP was noted.

The impact of nurse office-day SBP independent of day or 24 hour SBP on target organ changes was mainly noted in the highest quartile of nurse office-day SBP in all participants (Tables 3.4-3.6) and in sensitivity analysis conducted across quartiles in those with a normotensive day BP and in hypertensives separately (Tables 3.4-3.7). In this regard, as compared to the lowest quartile of nurse office-day SBP, marked increases in multivariate adjusted (including adjustments for day and 24-hour SBP) LVMI and PWV were noted in the highest quartile of nurse office-day SBP in all participants, in normotensives only and in hypertensives only (Tables 3.4-3.7). Moreover, as compared to the lowest quartile of nurse office-day SBP, marked increases in the proportion of participants with an increased LVMI and PWV were noted in the highest quartile of nurse office-day SBP in all participants (Table 3.4, LVMI: Odds ratio=1.46, confidence intervals=1.10-1.93, $p<0.01$; PWV; Odds ratio=1.80, confidence intervals=1.01-3.23, $p<0.05$) and in hypertensives only (Table 3.7, LVMI: Odds ratio=1.76, confidence intervals=1.18-2.62, $p<0.01$; PWV; Odds ratio=1.74, confidence intervals=1.18-2.62, $p<0.01$; PWV; Odds ratio=1.74, confidence intervals=1.10-2.76, $p<0.05$), but these

Table 3.3. Unadjusted (Pearson's r) and multivariate adjusted (Partial r) relationships between isolated increases in in-office BP with nurse BP measurements (nurse office minus day systolic blood pressure [SBP]) and target organ changes.

<u>Nurse office minus day</u> <u>SBP vs</u>	Adjustments*	Pearson's or Partial r	CI	p-values [†]
<u>All participants</u>				
LVMI (n=464)	Unadjusted	0.29	0.20 to 0.37	<0.0001
	*+ day SBP	0.15	0.06 to 0.24	<0.01
	*+ 24-Hour SBP	0.14	0.05 to 0.23	<0.01
Aortic PWV (n=662)	Unadjusted	0.43	0.36 to 0.49	<0.0001
	*+ day SBP	0.22	0.14 to 0.29	<0.0001
	*+ 24-Hour SBP	0.21	0.13 to 0.28	<0.0001
<u>Normal day BP</u>				
LVMI (n=269)	Unadjusted	0.27	0.15 to 0.37	<0.0001
	*+ day SBP	0.18	0.06 to 0.29	<0.005
	*+ 24-Hour SBP	0.16	0.04 to 0.27	<0.05
Aortic PWV (n=402)	Unadjusted	0.43	0.35 to 0.51	<0.0001
	*+ day SBP	0.18	0.09 to 0.28	<0.0001
	*+ 24-Hour SBP	0.18	0.09 to 0.28	=0.0005
<u>Hypertensives</u>				
LVMI (n=209)	Unadjusted	0.22	0.09 to 0.35	<0.005
	*+ day SBP	0.19	0.05 to 0.32	<0.01
	*+ 24-Hour SBP	0.19	0.06 to 0.32	<0.01
Aortic PWV (n=290)	Unadjusted	0.26	0.15 to 0.36	<0.0001
	*+ day SBP	0.21	0.09 to 0.32	<0.001
	*+ 24-Hour SBP	0.20	0.08 to 0.31	<0.005

LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants and hypertensives), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). [†]Further adjusted for non-independence of family members.

Table 3.4. Multivariate adjusted (including adjustments for 24-hour systolic blood pressure [SBP]) target organ changes and proportion with target organ changes above thresholds across quartiles of nurse office-day SBP (isolated increases in in-office SBP with nurse measurement). See Table 3.5 for unadjusted values and Table 3.6 for adjustments for day SBP.

		Quartiles of nurse office-day SBP (mm Hg) [#]				p-values*		
		1	2	3	4	4 vs 1	4 vs 2	3 vs 1
<u>All participants</u>								
Nurse office-day SBP (mm Hg)	Mean (±SD) (n) [#]	-11.7±6.4 (187)	-0.5±2.5(188)	9.0±3.4(187)	26.4±10.7(188)			
	Range (mm Hg) [#]	<-5.1	≥-5.1 to 3.5	≥3.5 to 14.8	≥14.8			
LVMI (g/m ^{2.7})(n)		39.8±12.2(129)	41.9±11.9(106)	42.9±11.7(124)	46.1±12.4(104)	<0.0005	<0.02	<0.05
PWV (m/sec)(n)		5.85±2.23(172)	6.26±1.94(168)	6.29±1.90(160)	7.21±2.42(162)	<0.0001	<0.001	<0.05
n (%) LVMI>51 g/m ^{2.7}		12 (9.3)	15 (14.2)	25 (20.2)	40 (38.5)	<0.01 ^{††}	=0.07	=0.42
n (%) PWV>10 m/sec		2 (1.2)	1 (0.6)	10 (6.3)	36 (22.2)	<0.05 ^{††}	<0.05	=0.57
<u>Normal day BP</u>								
Nurse office-day SBP (mm Hg)	Mean (±SD) (n) [#]	-11.2±5.2(112)	-2.3±2.1(112)	5.1±2.7(112)	20.7±9.6(111)			
	Range (mm Hg) [#]	<-5.7	≥-5.7 to 1.2	≥1.2 to 10.9	≥10.9			
LVMI (g/m ^{2.7})(n)		36.2±10.3(75)	37.7±10.0(63)	41.9±9.8(70)	42.7±10.9(61)	=0.001	<0.05	<0.001
PWV (m/sec)(n)		4.91±1.72(102)	5.38±1.51(102)	5.46±1.39(98)	6.29±1.90(100)	<0.0001	<0.001	<0.05
n (%) LVMI>51 g/m ^{2.7}		2 (2.7)	5 (7.9)	10 (14.3)	12 (19.7)	=0.11	=0.67	=0.09
n (%) PWV>10 m/sec		0 (0)	0 (0)	1 (1.0)	10 (10.0)	_**	_**	_**

LVMI, left ventricular mass index; PWV, pulse wave velocity. *Adjustments are for 24-hour SBP, age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). Probability values were further adjusted for non-independence of family members. **Could not be determined. [#]Determined from all 750 participants or those with a normal day BP. ^{††}See text for odds ratios and confidence intervals for quartile 4 vs 1.

Table 3.5. Unadjusted target organ changes across quartiles of nurse office-day systolic blood pressure (SBP) (isolated increases in in-office BP with nurse BP measurements).

		Quartiles of nurse office-day SBP (mm Hg) [#]				p-values [†]		
		1	2	3	4	4 vs 1	4 vs 2	3 vs 1
<u>All participants</u>								
Nurse office-	Mean (±SD) (n) [#]	-11.7±6.4 (187)	-0.5±2.5(188)	9.0±3.4(187)	26.4±10.7(188)			
day SBP (mm Hg)	Range (mm Hg) [#]	<-5.1	≥-5.1 to 3.5	≥3.5 to 14.8	≥14.8			
LVMI (g/m ^{2.7})(n)		38.1±12.4(129)	40.5±12.6(106)	43.9±12.5(124)	48.4±12.4(104)	<0.0001	<0.0001	<0.0005
PWV (m/sec)(n)		5.27±2.36(172)	5.64±2.33(168)	6.43±2.28(160)	8.50±2.29(162)	<0.0001	<0.0001	<0.0001
<u>Normal day BP</u>								
Nurse office-	Mean (±SD) (n) [#]	-11.2±5.2(112)	-2.3±2.1(112)	5.1±2.7(112)	20.7±9.6(111)			
day SBP (mm Hg)	Range (mm Hg) [#]	<-5.7	≥-5.7 to 1.2	≥1.2 to 10.9	≥10.9			
LVMI (g/m ^{2.7})(n)		36.2±9.5(75)	38.1±12.4(63)	41.6±11.5(70)	44.0±10.2(61)	<0.0001	<0.005	<0.005
PWV (m/sec)(n)		4.72±1.32(102)	5.20±1.29(102)	5.35±1.48(98)	7.00±2.70(100)	<0.0001	<0.0001	<0.005

LVMI, left ventricular mass index; PWV, pulse wave velocity. [#]Determined from all 750 participants or those with a normal day BP.

Table 3.6. Multivariate adjusted (including adjustments for day systolic blood pressure [SBP]) target organ changes across quartiles of nurse office-day SBP (isolated increases in in-office BP with nurse BP measurements).

		Quartiles of nurse office-day SBP (mm Hg) [#]				p-values [†]		
		1	2	3	4	4 vs 1	4 vs 2	3 vs 1
<u>All participants</u>								
Nurse office-	Mean (±SD) (n) [#]	-11.7±6.4 (187)	-0.5±2.5(188)	9.0±3.4(187)	26.4±10.7(188)			
day SBP (mm Hg)	Range (mm Hg) [#]	<-5.1	≥-5.1 to 3.5	≥3.5 to 14.8	≥14.8			
LVMI (g/m ^{2.7})(n)		39.7±12.3(129)	41.9±1.16(106)	43.0±11.7(124)	46.1±12.4(104)	<0.0005	<0.05	<0.05
PWV (m/sec)(n)		5.87±2.36(172)	6.32±1.94(168)	6.32±1.90(160)	7.27±2.54(162)	<0.0001	<0.001	=0.08
<u>Normal day BP</u>								
Nurse office-	Mean (±SD) (n) [#]	-11.2±5.2(112)	-2.3±2.1(112)	5.1±2.7(112)	20.7±9.6(111)			
day SBP (mm Hg)	Range (mm Hg) [#]	<-5.7	≥-5.7 to 1.2	≥1.2 to 10.9	≥10.9			
LVMI (g/m ^{2.7})(n)		36.7±10.5(75)	37.6±10.2(63)	42.0±10.0(70)	42.1±10.8(61)	<0.01	<0.05	<0.005
PWV (m/sec)(n)		4.89±1.82(102)	5.37±1.51(102)	5.47±1.39(98)	6.31±2.00(100)	<0.0001	<0.001	<0.05

LVMI, left ventricular mass index; PWV, pulse wave velocity. *Adjustments are for day SBP, age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). [†]Further adjusted for non-independence of family members. [#]Determined from all 750 participants or those with a normal day BP.

Table 3.7. Target organ changes and proportion with target organ changes above thresholds across quartiles of nurse office-day systolic blood pressure (SBP)(isolated increases in in-office BP with nurse BP measurements) in hypertensives.

		Quartiles of nurse office-day SBP (mm Hg) [#]				p-values [†]		
Adjustments*		1	2	3	4	4 vs 1	4 vs 2	3 vs 1
Nurse office-day SBP (mm Hg)								
Mean (±SD) (n) [#]		-5.1±6.5 (85)	8.9±3.3 (84)	18.3±2.9 (84)	35.1±10.0 (85)			
Range (mm Hg) [#]		<3.3	≥3.3 to 13.7	≥13.7 to 24.5	≥24.5			
LVMI (g/m ^{2.7})(n)	Unadjusted	43.8±17.1 (55)	43.8±11.5 (61)	47.9±20.4 (53)	52.3±13.3 (41)	<0.005	<0.01	=0.12
	*+ day SBP	43.7±13.8	44.3±12.9	48.3±13.2	51.1±13.3	<0.05	<0.05	=0.09
	*+ 24-Hour SBP	43.2±13.6	44.4±12.8	48.3±13.2	51.1±13.3	<0.01	<0.02	=0.05
PWV (m/sec)(n)	Unadjusted	6.92±2.89 (76)	7.03±2.31 (71)	8.09±3.08 (69)	9.58±3.48 (75)	<0.0001	<0.0001	<0.05
	*+ day SBP	7.29±2.96	7.47±2.35	7.75±2.33	9.13±2.85	<0.001	<0.0005	=0.31
	*+ 24-Hour SBP	7.42±2.79	7.47±2.35	7.70±2.33	9.05±2.77	<0.005	<0.0005	=0.51
n (%) LVMI>51 g/m ^{2.7}		10 (18.2)	12 (19.7)	20 (37.7)	21 (51.2)	<0.01**	<0.05**	<0.05**
n (%) PWV>10 m/sec		3 (3.9)	3 (4.2)	14 (20.3)	24 (32.0)	<0.05**	<0.05**	<0.05**

LVMI, left ventricular mass index; PWV, pulse wave velocity. *Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension, regular tobacco use, regular alcohol intake and office mean arterial pressure (MAP) (for PWV only). [†]Further adjusted for non-independence of family members.

[#]Determined from all 338 hypertensives. ** Adjusted for 24-hour SBP, but not MAP.

differences did not achieve significance in normotensives only (Table 3.4). Sensitivity analysis conducted in those not receiving antihypertensive medication and without age in the regression model, produced essentially the same outcomes (Table 3.8).

3.3.5 Quantitative impact of nurse office-day BP on target organ changes.

In a multivariate model with all potential confounders forced into the model, the impact (standardized β -coefficient or slope of relationship) of nurse office-day SBP on LVMI or PWV and the risk of an increased LVMI or PWV was at least equivalent to the impact of day, night or 24-hour SBP (Table 3.9).

3.4 Discussion

The main findings of the present study are as follows: First, in a randomly selected community sample, an increased difference between nurse-derived in-office and day SBP (nurse office-day SBP), an index of isolated increases in in-office BP (or white-coat effects), was related to both LVMI and aortic PWV independent of confounders and ambulatory day and 24-hour SBP. These relationships were reproduced in those with normotensive day BP values and hypertensive participants separately and the quantitative effect of nurse office-day SBP on target organ changes was similar to that for ambulatory SBP. Second, nurse-derived office SBP was as strongly associated with target organ changes as ambulatory SBP, and independent of ambulatory SBP, findings that are likely to be accounted for by the independent relationship between nurse office-day SBP and target organ changes.

To the best of my knowledge, the present study is the first to report on the extent to which nurse office-day SBP, an index of isolated in-office increases in BP, is related to target organ damage independent of day or 24-hour SBP. Although a number of studies have demonstrated that isolated increases in in-office BP are related to organ damage or cardiovascular outcomes (Verdecchia et al 2005, Mancia et al 2006, Kuwajima et al 1993,

Table 3.8. Target organ changes and proportion with target organ changes above thresholds across quartiles of nurse office-day systolic blood pressure (SBP)(isolated increases in in-office BP with nurse BP measurements) in those not receiving antihypertensive therapy and without age as an adjustor.

Adjustments*		Quartiles of nurse office-day SBP (mm Hg) [#]				p-values [†]		
		1	2	3	4	4 vs 1	4 vs 2	3 vs 1
Nurse office-day SBP (mm Hg)								
	Mean (±SD) (n) [#]	-12.5±6.5 (145)	-2.1±2.3 (144)	5.9±2.9 (144)	21.7±9.6 (145)			
	Range (mm Hg) [#]	<-5.9	≥-5.9 to 1.6	≥1.6 to 11.9	≥11.9			
LVMI (g/m ^{2.7})(n)	Unadjusted	37.3±10.5(101)	40.1±15.2(81)	42.5±11.9(90)	45.3±13.4 (84)	<0.0001	<0.01	=0.005
	*+ day SBP	37.7±10.8	39.5±11.2	43.1±11.0	43.7±11.0	<0.0005	<0.05	<0.001
	*+ 24-Hour SBP	37.5±10.8	39.5±11.2	43.2±11.0	43.8±11.0	=0.0001	<0.02	=0.0005
PWV (m/sec)(n)	Unadjusted	5.04±1.71(132)	5.34±1.44(130)	5.68±1.81(123)	7.55±3.01(127)	<0.0001	<0.0001	<0.05
	*+ day SBP	5.07±2.30	5.65±1.94	5.74±1.88	7.14±2.37	<0.0001	<0.0001	<0.05
	*+ 24-Hour SBP	4.98±2.41	5.61±1.94	5.77±1.88	7.24±2.48	<0.0001	<0.0001	<0.01
n (%) LVMI>51 g/m ^{2.7}		7 (6.9)	11 (13.6)	17 (18.9)	22 (26.2)	<0.01**	<0.72**	<0.05**
n (%) PWV>10 m/sec		2 (1.5)	1 (0.8)	3 (2.4)	20 (15.7)	<0.005**	<0.01**	=0.35**

LVMI, left ventricular mass index; PWV, pulse wave velocity. *Adjustments are for sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension, regular tobacco use, regular alcohol intake and office mean arterial pressure (MAP) (for PWV only). [†]Further adjusted for non-independence of family members. [#]Determined from all 578 participants not receiving antihypertensive therapy. ** Adjusted for 24-hour SBP, but not MAP.

Table 3.9. Quantitative impact (standardized β -coefficient or slope of relationship) of nurse office-day systolic blood pressure (SBP) (isolated increases in in-office SBP with nurse measurement) on target organ changes as compared to the effects of ambulatory SBP.

<u>SBP included in the multivariate models</u>						
	Day SBP		Night SBP		24-hour SBP	
	β -coeff. $\pm$ SEM	p value [†]	β -coeff. $\pm$ SEM	p value [†]	β -coeff. $\pm$ SEM	p value [†]
<u>Left ventricular mass index (g/m^{2.7}) vs (n=463)</u>						
SBP Nurse office-day	0.15 $\pm$ 0.05	<0.005	0.13 $\pm$ 0.05	<0.01	0.15 $\pm$ 0.05	<0.005
SBP Day	0.16 $\pm$ 0.05	<0.001	-	-	-	-
SBP Night	-	-	0.14 $\pm$ 0.05	<0.005	-	-
SBP 24-Hour	-	-	-	-	0.16 $\pm$ 0.05	<0.001
<u>Aortic pulse wave velocity vs (n=662)</u>						
SBP Nurse office-day	0.30 $\pm$ 0.05	<0.0001	0.16 $\pm$ 0.04	<0.0005	0.26 $\pm$ 0.05	<0.0001
SBP Day	0.34 $\pm$ 0.05	<0.0001	-	-	-	-
SBP Night	-	-	0.21 $\pm$ 0.04	<0.0001	-	-
SBP 24-Hour	-	-	-	-	0.32 $\pm$ 0.05	<0.0001
<u>Left ventricular mass index >51 g/m^{2.7} vs (n=463)</u>						
SBP Nurse office-day	0.14 $\pm$ 0.05	<0.005	0.13 $\pm$ 0.05	<0.01	0.14 $\pm$ 0.05	<0.01
SBP Day	0.09 $\pm$ 0.05	=0.06	-	-	-	-
SBP Night	-	-	0.08 $\pm$ 0.05	=0.11	-	-
SBP 24-Hour	-	-	-	-	0.09 $\pm$ 0.05	=0.07
<u>Aortic pulse wave velocity >10 m/sec vs (n=662)</u>						
SBP Nurse office-day	0.31 $\pm$ 0.06	<0.0001	0.17 $\pm$ 0.05	<0.001	0.28 $\pm$ 0.06	<0.0001
SBP Day	0.37 $\pm$ 0.06	<0.0001	-	-	-	-
SBP Night	-	-	0.25 $\pm$ 0.05	<0.0001	-	-
SBP 24-Hour	-	-	-	-	0.36 $\pm$ 0.06	<0.0001

β -coeff., Standardized β -coefficient (slope of standardized relationships). Multivariate models included office-day SBP, either day, night or 24-hour SBP, age, sex, body weight (for LVMI), body mass index (for PWV) the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension, regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). [†]Further adjusted for non-independence of family members.

Glen et al 1996, Muscholl et al 1998, Owens et al 1998, Palatini et al 1998, Landray et al 1999, O'Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Sega et al 2001, Palatini et al 1997), none of these studies evaluated the impact of nurse-elicited isolated increases in in-office BP. In this regard, nurse-elicited isolated increases in in-office BP are less evident than that of physicians (Little et al 2002) and this has been employed as a potential explanation for the finding that nurse-derived BP values are often as closely associated with organ damage as out-of-office ambulatory BP (Nystrom et al 2005, Veerman et al 1996, de Blok et al 1991, Jula et al 1999, Moran et al 2006, Woodiwiss et al 2009). In the present study, I show that although nurse office-day BP values are quantitatively similar to that previously described (Little et al 2002), that the closeness of the relationship between high quality nurse-derived BP and target organ changes, relationships equivalent to that noted between ambulatory BP and organ changes, can in-part be attributed to the independent relationship between nurse-elicited isolated increases in in-office BP and organ damage, independent of ambulatory BP. Thus, even under the best conditions with nurses as opposed to physicians measuring BP, in-office BP values in-part reflect the impact of a phenomenon that cannot be attributed to that of the effects of BP *per se* (isolated increases in in-office BP) on organ damage.

In the present study, the multivariate adjusted correlation coefficients for the nurse office-day BP-target organ changes were not particularly strong (partial $r=0.14-0.21$), possibly as a consequence of colinearity between adjustors. This should nevertheless not detract from the potential impact of nurse office-day BP on target organ changes. Indeed, unadjusted and multivariate-adjusted LVMI and PWV in the upper quartile of nurse office-day SBP were markedly greater than those noted in the lower quartile. Moreover, the slope (standardised β -coefficient) of the nurse office-day BP versus target organ relations was similar to the slope of the relations between ambulatory BP and target organ changes when these variables were considered in the same multivariate models. The nurse office-day versus target organ relationships also explain the limited effect of adjustments for ambulatory BP on nurse-derived office BP versus target organ relationships.

Importantly, although one other study has demonstrated that office-day BP determines target organ changes (Palatini et al 1997), the office-day SBP values in that study suffered from the previously described limitation (Parati et al 1998) of an inverse relationship with day SBP. Furthermore, in that study (Palatini et al 1997) whether office-day BP values were related to office-day heart rate, relationships which should occur if office-day SBP in-part reflects an autonomic response, is uncertain. In this regard, previous studies have questioned whether office-day BP-heart rate relationships do indeed occur (Parati et al 1998). In contrast, in the present study nurse office-day BP was not inversely associated with day BP, and was directly correlated with office-day heart rate. Thus, in the present study at least, it is possible that nurse-elicited office-day BP may in-part reflect a dysregulated autonomic response. However, although office-day BP may correlate with alterations that reflect autonomic dysregulation (Neumann et al 2005), office-day BP may not correlate with the alerting response ascertained from changes in beat-to-beat BP or heart rate on exposure of subjects to clinical personnel (Parati et al 1998).

A previous large study conducted in hypertensives (Parati et al 1998) suggesting that office-day BP is of pathological significance, demonstrated that the effects on organ changes occurred only at higher day BP values. These findings would suggest that office-day BP differences only have pathological significance in hypertensives and hence that an increased in-office but normal day BP is not a pathological condition. In contrast, in our community-based study we noted that nurse office-day SBP was related to target organ values within day BP ranges that would be considered as normotensive. These findings suggest that the office-day BP, as assessed from nurse-derived BP measurements, reflects a pathological condition even in the range of day BP values that may be considered as normal. However, caution should be exercised in interpreting the results of the present study, as we were not statistically powered to show an impact of nurse office-day BP on the proportion of participants with an increased LVMI or PWV above threshold values.

In the present study we show that although in-office BP is higher than day BP, in-office pulse rate is lower than day pulse rate. As with previous studies that have demonstrated dissociations between differences in in-office and day pulse rate versus BP (Parati et al 1998), it may be argued that in-office increases in BP do not reflect an alerting response normally attributed to sympathetic changes, as similar differences in pulse rate should be noted. However, day pulse rates are likely to be recorded during normal daily activities, whilst nurse recorded pulse rates are measured at rest. In contrast the higher BP values obtained in- as opposed to out-of-office are likely to reflect an emotional or psychological effect as opposed to the effects of daily activities. Thus, one should not expect the same differences in in-office and day BP versus pulse rate. Rather, if in-office BP in-part reflects an alerting response, a direct correlation between in-office-day BP and pulse rate should be noted as described in the present study. Although the correlation coefficient for this relationship was robust ($p < 0.0001$), it cannot be considered to be strong ($r = 0.17$). However, this is not surprising considering the confounding effect on pulse rate of differences in activity in the in- versus the out-of-office environment.

The clinical implications of the present study relate to the value of nurse-derived in-office BP measurements. As nurse-derived in-office BP measurements do not elicit as marked an isolated increase in in-office BP as physician-derived BP measurements (Little et al 2002), and as supported by the present and prior (Nystrom et al 2005, Veerman et al 1996, de Blok et al 1991, Jula et al 1999, Moran et al 2006, Woodiwiss et al 2009) studies, nurse-derived BP values are as closely correlated with organ damage as ambulatory BP, it has been suggested that nurse-derived BP measurements may be better than physician-derived BP measurements. However, the present study suggests that although as compared to out-of-office BP, nurse-derived BP may perform equally as well at indexing the extent of cardiovascular damage, a significant proportion of this may be through isolated increases in BP in the office. Hence, the present results suggest that nurse-derived BP measurements do not approximate the impact of BP effects *per se* on cardiovascular damage.

The limitations of the present study include the cross-sectional design and low response rates which precludes conclusions being drawn regarding cause and effect. Nevertheless, as decreases in office-day BP in response to antihypertensive therapy are not associated with improvements in target organ measures (Fagard et al 2000, Paratti et al 2000), it is likely that nurse office-day BP-target organ relationships are not accounted for by BP effects. However, intervention studies assessing whether antihypertensive therapy may modify specifically nurse-elicited increases in office-day BP and whether these changes are associated with on-treatment modifications in target organ damage, are still required. Second, the present study was conducted in one ethnic group, a group previously demonstrated to have a high prevalence of isolated increases in in-office BP (Maseko et al 2011 and chapter 2). Further studies with high quality in-office BP measurements conducted by a single nurse or technician-observer or with measurements well standardized across sites, are therefore required in alternative ethnic groups with a high prevalence of isolated increases in in-office BP to address this issue. Third, as PWV is strongly determined by pulse rate and aortic distending pressures, indexed by MAP; it is possible that isolated increases in in-office BP or pulse rate may translate into isolated increases in PWV simply through acute haemodynamic changes. However, in the present study relations between nurse office-day BP and PWV were noted after adjustments for MAP and pulse rate. However, this does not exclude the possibility of residual confounding effects. Nevertheless, nurse office-day BP was associated with LVMI, a target organ change that is independent of acute changes in distending pressures or heart rate such as occur in the in-office setting in participants with an increased nurse-day BP.

In conclusion, in the present study I show that nurse-elicited increases in office-day BP are associated with organ damage independent of ambulatory BP. Furthermore, I demonstrate that although high quality nurse-derived BP measurements may be as strongly associated with cardiovascular damage as ambulatory BP, this effect may be driven in-part by office-day BP. These data therefore suggest that high quality nurse-derived BP

measurements do not approximate the impact of BP effects *per se* on cardiovascular damage.

CHAPTER 4

Does an Attenuated Nocturnal Blood Pressure Dipping Explain the
Independent Relationship Between White-Coat Effects and Organ
Damage?

Abstract

The mechanisms that explain the relationship between nurse-elicited isolated increases in in-office blood pressure (BP)(office-day BP), an index of white-coat effects, and organ damage independent of ambulatory BP and additional confounders are uncertain. In the present study in 750 participants from a community sample I evaluated whether nurse office-day BP is inversely related to day-night BP (BP dipping) and whether this relationship may in-part explain the independent association between office-day BP and organ damage. Organ changes were assessed from carotid-femoral pulse wave velocity (PWV) (applanation tonometry and SphygmoCor software) (n=662) and left ventricular mass indexed to height^{2.7} (LVMI) (echocardiography)(n=463). Nurse office-day systolic BP (SBP) was correlated with day-night SBP ($r=-0.21$, $p<0.0001$), % night/day SBP ($r=0.22$, $p<0.0001$) and directly correlated with night SBP ($r=0.14$, $p=0.0001$) and these relationships persisted with adjustments for confounders including day SBP ($p<0.005$ for all). Although unadjusted and multivariate adjusted (including for day SBP) nurse office-day SBP was associated with LVMI (partial $r=0.15$, $p<0.01$) and PWV (partial $r=0.22$, $p<0.0001$), neither day-night SBP (LVMI; partial $r=-0.01$, $p=0.88$, PWV: partial $r=-0.04$, $p=0.30$) nor % night/day SBP (LVMI; partial $r=0.01$, $p=0.91$, PWV: partial $r=0.04$, $p=0.37$) were independently related to target organ changes. Moreover, the relationships between nurse office-day SBP and target organ changes persisted with adjustments for either day-night SBP (LVMI: partial $r=0.12$, $p<0.05$; PWV: partial $r=0.17$, $p<0.0001$) or night SBP (LVMI: partial $r=0.13$, $p<0.01$; PWV: partial $r=0.15$, $p=0.0001$). In conclusion, although nurse office-day SBP, an index of an alerting response, is independently associated with an attenuation of nocturnal decreases in SBP, neither a decreased BP dipping, nor nocturnal BP explain the independent relationship between nurse office-day SBP and target organ changes.

4.1 Introduction

Ambulatory blood pressure (BP) values are superior to in-office BP values in predicting cardiovascular outcomes (Perloff et al, 1983, 1989, Ohkubo et al 1994, Imai et al 1996, Redon et al 1998, Khattar et al 1999, Verdecchia et al, 1994, 1998, 2002, Staessen et al 1999, Robinson et al 2001, Clement et al 2003, Kikuya et al 2005, Dolan et al 2005, Fagard et al 2004, 2008, Hansen et al 2005, Ingelssen et al 2006, Dawes et al 2006, Schwartz et al 2007, Astrup et al 2007, Eguchi et al 2008, Palmas et al 2009, Dzrelinska et al 2009, Mesquita-Bastos et al 2010, Boggia et al 2011). These effects have been attributed in part to isolated increases in in-office BP (increased in-office compared to day BP often called white-coat effects or alerting responses). In this regard, meta-analyses (Hansen et al 2007, Fagard et al 2007) have demonstrated that an increased in-office, but normal out-of-office BP predicts cardiovascular outcomes to a similar extent as that of sustained normotension (normal in and out-of-office BP) and some studies have failed to demonstrate a relationship between isolated increases in in-office BP and organ damage (White et al 1998, Verdecchia et al 1992, Grosse et al 1993). Although alternative studies suggest a pathological role for isolated increases in in-office BP (Verdecchia et al 2005, Mancia et al 2006, Kuwajima et al 1993, Glen et al 1996, Palatini et al 1997, Muscholl et al 1998, Owens et al 1998, Palatini et al 1998, Landray et al 1999, O'Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Segal et al 2001, Maseko et al, chapter 3); decreases in the difference between office and day BP (an index of isolated increases in in-office BP) produced by antihypertensive therapy are unrelated to improvements in organ damage (Fagard et al 2000, Paratti et al 2000). Hence, although it is still unclear as to whether isolated increases in in-office BP contribute to risk prediction, it may be desirable to exclude these differences when implementing BP-lowering therapy as these differences may not reflect the impact of BP on cardiovascular damage. However, whether white-coat effects or isolated increases in in-office BP are entirely independent of BP is nevertheless still uncertain.

White-coat hypertension is associated with an attenuated decrease in nocturnal BP (BP dipping)(Bochud et al 2009). In this regard, a reduced BP dipping and nocturnal BP has an adverse prognostic impact in several populations (O'Brien et al 1988, Zweiker et al 1994, Verdecchia et al 1994, 1998, 2000, 2007, 2012, Ohkubo et al 1997, 1998, 2002, Yamamoto et al 1998, Nakano et al 1998, 2004, Clement et al 2003, Sega et al 2005, Staessen et al 1999, Dolan et al 2005, 2009, Fagard et al 2004, 2005, 2008a, 2008b, 2009, Boggia et al 2007, Ingelsson et al 2006, Kario et al 2001, Ben-Dov et al 2007, Astrup et al 2007, Schwartz et al 2007, Brotman et al 2008, Ishikawa et al 2008, de la Sierra et al 2009, Fan et al 2010, Kikuya et al 2005, Palmas et al 2009, Ungar et al 2009, Bouhanick et al 2008, Dzielinska et al 2009, Muxfedlt et al 2009, Mesquite-Bastos et al 2010) and is independently associated with target organ damage (Verdecchia et al 1990, Kuwajima et al 1992, Kawamoto et al 1991, Kario et al 1996). It is therefore possible that the relationship between isolated increases in in-office BP or white-coat effects and organ damage may be attributed to the adverse effects of an attenuated nocturnal BP dipping, or from nocturnal BP independent of day BP. In the present study I therefore evaluated whether nurse office-day BP is inversely related to day-night or the % day/night BP (BP dipping) and whether this relationship may in-part explain the independent association between office-day BP and organ damage.

4.2 Methods

4.2.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The study design has largely been described in chapter 2 (section 2.2.1). The details of the households and participants recruited as well as the sample sizes of participants with measurements that

were either performed or met with prespecified quality control criteria are given in chapter 3 (section 3.2.1).

4.2.2 Clinical, demographic and anthropometric measurements.

A standardized questionnaire was administered to obtain demographic and clinical data as described in chapter 2 (section 2.2.2). Details of anthropometric measurements and the blood tests performed are given in chapter 3 (section 3.2.2). As indicated in preceding chapters, diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA_{1c} value greater than 6.1% (see section 2.2.2).

4.2.3 Blood pressure.

High quality conventional BP measurements were obtained by one trained nurse according to guidelines using a standard mercury sphygmomanometer as described in chapter 2 (section 2.2.3). Details of the data defining the quality of measurements are given in chapter 3 (section 3.2.3). Hypertension was defined as a mean BP $\geq 140/90$ mm Hg or the use of antihypertensive medication. Ambulatory 24-hour, day and night BP were determined using SpaceLabs monitors (model 90207) as described in chapter 2 (section 2.2.3). The average ($\pm$ SD) number of BP recordings obtained are described in chapter 3 (section 3.2.3).

4.2.4 Measures of target organ changes

4.2.4.1 Pulse wave velocity.

Aortic stiffness was estimated using carotid-femoral (aortic) pulse wave velocity (PWV). Carotid-femoral PWV has been demonstrated in a number of studies to predict

cardiovascular outcomes independent of traditional risk factors including CBP.(O'Rourke et al 2002). Carotid-femoral PWV was determined as described in chapter 3 (section 3.2.4.1).

4.2.4.2 Echocardiography.

Echocardiographic measurements were performed using previously described methods on the same echocardiogram (HP-5500, Palo Alto, Ca) (Norton et al 2008, Woodiwiss et al 2008, Libhaber et al 2008, Woodiwiss et al 2009). All measurements were recorded and analyzed by two experienced investigators (CL and AJW) whom were unaware of the clinical data of the participants. Left ventricular (LVM) mass was determined using 2-dimensional targeted M-mode echocardiography as described in chapter 3 (section 3.2.4.2). Left ventricular mass was derived according to an anatomically validated formula (Devereux et al 1986) ($LVM = 0.8 \times [1.04 (LVEDD + IVS + PWT)^3 - (LVEDD)^3] + 0.6g$) and indexed to height^{2.7} (LVM index, LVMI). Left ventricular hypertrophy (LVH) was defined as a LVMI >51 g/m^{2.7} for both women and men (Nunez et al 2005). The intra- and inter-observer variability for LV dimension measurements employed to calculate LVMI have been described in chapter 3 (section 3.2.4.2).

4.2.5 Data analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Data are shown as mean±SD or mean±SEM. Means and proportions were compared by the large-sample z-test and the χ^2 -statistic, respectively. Relationships were determined using multivariate regression analysis with appropriate confounders included in each model. Adjustments were made for the impact of day, night or day-night BP, age, sex, body weight (for LVMI) or BMI (for PWV), the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake. When assessing relationships with PWV,

office mean arterial pressure (distending pressure) was also included as an adjustor. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package).

4.3 Results

4.3.1 General characteristics of participants.

The characteristics of the study group with and without ambulatory BP measurements that met with prespecified quality control criteria are shown in chapter 3 (Tables 3.1 and 3.2). The office, day and night BP values and the nurse office-day BP values are given in chapter 3 (Table 3.2). The nocturnal decreases in BP (absolute or % of day) of the study group are given in Table 4.1.

4.3.2 Relationship between nurse office-day BP and BP dipping

On bivariate analysis, nurse office-day systolic or diastolic BP was inversely related to day-night or % night/day systolic and diastolic BP (BP dipping) (Figure 4.1). With adjustments for potential confounders and day SBP or DBP these relationships persisted (Table 4.2).

4.3.3 Relationship between BP dipping or nocturnal BP and target organ changes

Although decreases in BP at night or % night/day (BP dipping) were associated with LVMI and PWV in unadjusted analyses, with adjustments for 24-hour, neither night nor %night/day BP were independently associated with LVMI or PWV (Tables 4.3 and 4.4). Although night BP was associated with LVMI and PWV in unadjusted analyses, with

adjustments for day BP, night BP was not independently associated with LVMI and only a trend for significance was noted with PWV (Table 4.5).

Table 4.1 Nocturnal decreases in blood pressure in the study group.

	All	Echo	Pulse wave
	<u>All participants</u>		
Sample size (n)	750	463	662
Day-night systolic BP (mm Hg)	11.2±10.5	11.4±10.7	11.2±10.5
Day-night diastolic BP (mm Hg)	12.6±8.1	12.8±8.4	12.7±8.0
% night/day systolic BP* (mm Hg)	90.9±8.3	90.8±8.4	90.8±8.3
% Day/night diastolic BP* (mm Hg)	83.8±10.2	83.7±10.5	83.7±10.1
n (%) Non-dippers†	142 (18.9)	92 (19.9)	123 (18.6)
(≤2.36/2.73 Hg day-night SBP/DBP)†			
	<u>Untreated participants</u>		
Sample size (n)	578	356	512
Day-night systolic BP (mm Hg)	12.1±9.4	12.7±9.6	12.2±9.5
Day-night diastolic BP (mm Hg)	13.5±7.8	13.9±8.2	13.5±7.7
% night/day systolic BP* (mm Hg)	90.1±7.4	89.7±7.5	90.0±7.4
% Day/night diastolic BP* (mm Hg)	82.7±9.6	82.2±10.0	82.5±9.6
n (%) Non-dippers†	88 (15.2)	53 (14.9)	77 (15.0)
(≤2.36/2.73 Hg day-night SBP/DBP)†			

Echo, with echocardiography; Pulse wave, with pulse wave velocity. *Day expressed as a % of day BP, †determined from threshold values (lower 95% confidence intervals) noted in 158 healthy participants without hypertension or diabetes mellitus (no medication and HbA1c<6.1%), with a BMI<30 kg/m² who do not smoke or consume alcohol regularly and with normal blood results.

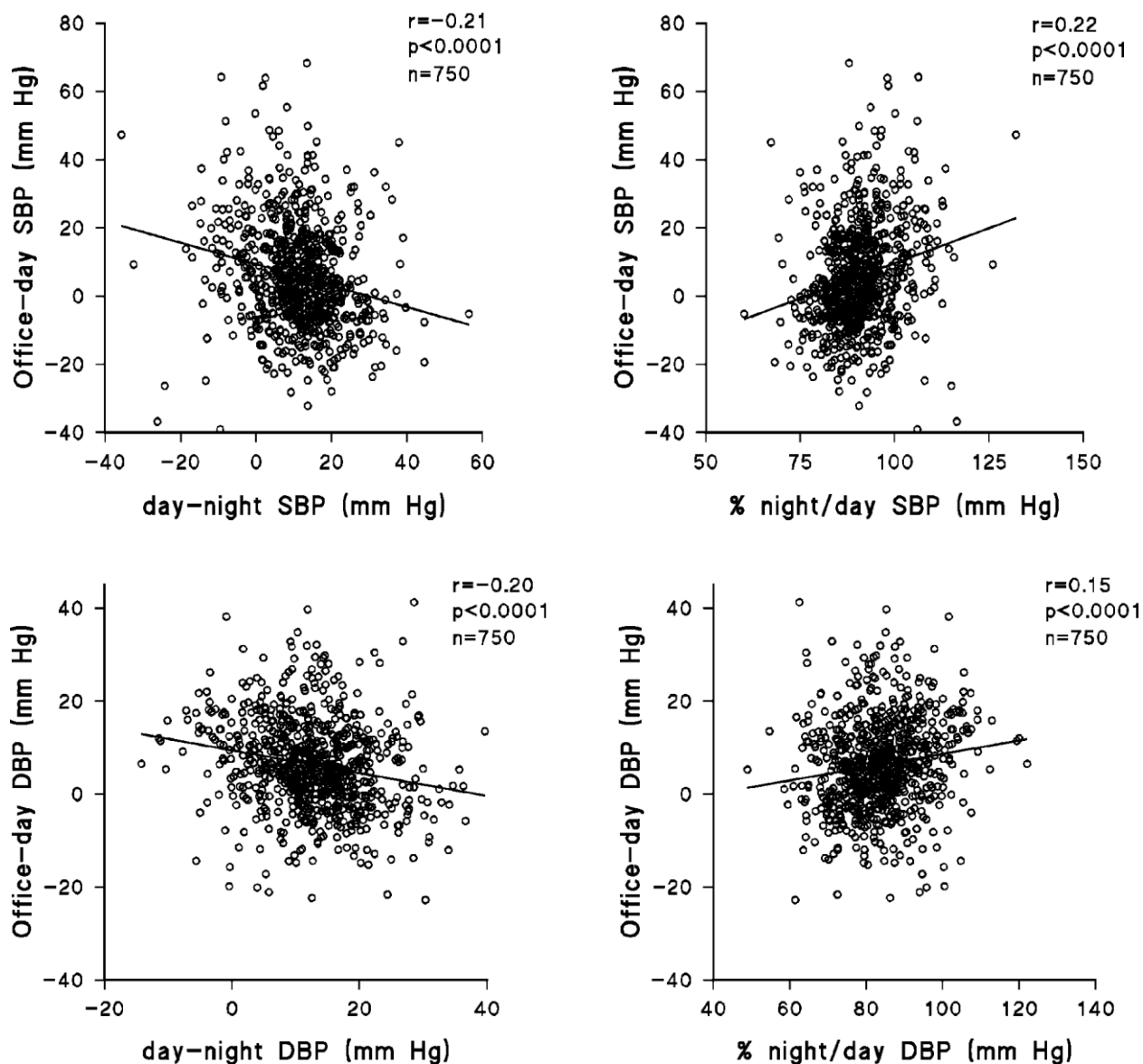


Figure 4.1. Bivariate relationships between isolated in-office increases in blood pressure (BP) or white-coat effects as indexed by office-day BP and nocturnal decreases in BP as indexed by day-night BP or % night/day BP. SBP, systolic BP; DBP, diastolic BP.

Table 4.2. Multivariate adjusted relationships between isolated increases in in-office BP or white-coat effects, as indexed by office-day blood pressure (BP) and nocturnal decreases in BP as indexed by day-night BP or % night/day BP.

	Adjustors	Partial r	(CI)	p value
Office SBP-Day SBP vs				
Day-Night SBP	+*	-0.13	-0.20 to -0.06	<0.0005
Day-Night SBP	Day SBP +*	-0.11	-0.18 to -0.04	<0.005
% Night/day SBP	+*	0.12	0.05 to 0.19	<0.001
% Night/day SBP	Day SBP +*	0.11	0.04 to 0.18	<0.005
Office DBP-Day DBP vs				
Day-Night DBP	+*	-0.17	-0.24 to -0.10	<0.0001
Day-Night DBP	Day DBP +*	-0.09	-0.16 to -0.01	<0.05
% Night/day DBP	+*	0.11	0.03 to 0.18	<0.005
%Night/day DBP	Day DBP +*	0.08	0.01 to 0.15	<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure. *Adjustments are for age, sex, waist circumference, diabetes mellitus or an HbA1c>6.5%, and treatment for hypertension. Probability values were further adjusted for non-independence of family members.

Table 4.3. Unadjusted (Pearson's r) and multivariate adjusted (Partial r) relationships between nocturnal decreases in systolic (SBP) and diastolic (DBP) blood pressure as assessed from day-night BP and target organ changes.

<u>Day-night SBP or DBP vs</u>	Adjustments*	Pearson's or Partial r	CI	p-values [†]
<u>Day-night SBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	-0.11	-0.20 to -0.02	<0.05
	*+ 24-Hour SBP	-0.01	-0.10 to 0.08	=0.88
Aortic PWV (n=662)	Unadjusted	-0.18	-0.25 to -0.10	<0.00001
	*+ 24-Hour SBP	-0.04	-0.12 to 0.03	=0.30
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	-0.04	-0.15 to 0.06	=0.42
	*+ 24-Hour SBP	0.02	-0.09 to 0.12	=0.47
Aortic PWV (n=512)	Unadjusted	-0.15	-0.23 to -0.06	<0.001
	*+ 24-Hour SBP	-0.07	-0.16 to 0.02	=0.12
<u>Day-night DBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	-0.16	-0.25 to -0.07	<0.0005
	*+ 24-Hour DBP	-0.07	-0.16 to 0.03	=0.25
Aortic PWV (n=662)	Unadjusted	-0.18	-0.26 to -0.11	<0.0001
	*+ 24-Hour DBP	-0.05	-0.13 to 0.03	=0.22
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	-0.10	-0.20 to 0.005	=0.06
	*+ 24-Hour DBP	-0.04	-0.14 to 0.07	=0.75
Aortic PWV (n=512)	Unadjusted	-0.15	-0.23 to -0.06	<0.001
	*+ 24-Hour DBP	-0.06	-0.15 to 0.03	=0.21

LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants and hypertensives), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only).

[†]Further adjusted for non-independence of family members.

Table 4.4. Unadjusted (Pearson's r) and multivariate adjusted (Partial r) relationships between nocturnal decreases in systolic (SBP) and diastolic (DBP) blood pressure as assessed from % night/day BP and target organ changes.

<u>% night/day</u> <u>SBP or DBP vs</u>	Adjustments*	Pearson's or Partial r	CI	p-values [†]
<u>% Night/day SBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	0.14	0.05 to 0.23	<0.005
	*+ 24-Hour SBP	0.01	-0.08 to 0.10	=0.91
Aortic PWV (n=662)	Unadjusted	0.22	0.15 to 0.29	<0.00001
	*+ 24-Hour SBP	0.04	-0.04 to 0.11	=0.37
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	0.08	-0.02 to 0.19	=0.12
	*+ 24-Hour SBP	-0.03	-0.13 to 0.08	=0.41
Aortic PWV (n=512)	Unadjusted	0.20	0.11 to 0.28	<0.0001
	*+ 24-Hour SBP	0.07	-0.02 to 0.15	=0.13
<u>% Night/day DBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	0.18	0.09 to 0.27	<0.0001
	*+ 24-Hour DBP	0.05	-0.04 to 0.14	=0.39
Aortic PWV (n=662)	Unadjusted	0.24	0.17 to 0.31	<0.0001
	*+ 24-Hour DBP	0.05	-0.03 to 0.12	=0.26
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	0.13	0.02 to 0.23	<0.05
	*+ 24-Hour DBP	0.04	-0.09 to 0.12	=0.92
Aortic PWV (n=512)	Unadjusted	0.23	0.14 to 0.31	<0.0001
	*+ 24-Hour DBP	0.06	-0.03 to 0.14	=0.25

LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants and hypertensives), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only).

[†]Further adjusted for non-independence of family members.

4.3.4 Relationship between alerting response (white-coat effects) and target organ changes

Nurse office-day systolic BP (alerting response) was independently associated with LVMI and PWV (Figure 4.2) and these relationships were unaffected by adjustments for either BP dipping (day-night or % night/day BP) or night BP (Figure 4.2).

4.4 Discussion

The main findings of the present study are as follows: Although nurse-elicited isolated increases in in-office BP or white coat effects, as indexed by nurse office-day BP, are independently associated with an attenuated nocturnal BP decline, neither BP dipping nor night BP can explain the independent relationships between nurse-elicited isolated increases in in-office BP and target organ changes as assessed from left ventricular mass index and aortic pulse wave velocity.

Although prior studies have demonstrated a strong and independent relationship between white-coat effects as indexed by office-day BP, and an attenuated decline in BP at night (Bochud et al 2009), to the best of my knowledge the present study is the first to show that this relationship is unlikely to explain the impact of isolated in office BP or white-coat effects on organ damage. In this regard, in the present study, although I was able to show that nurse office-day BP was inversely related to day-night or % night/day BP, indices of nocturnal decreases in BP, neither day-night, nor % night/day BP were independently associated with either LVMI or aortic PWV and adjustments for either day-night, or % night/day BP failed to modify the independent relationships between nurse office-day BP (alerting response) and target organ changes. In addition, in the present community, night BP was only modestly associated with target organ changes independent of day BP and adjustments for night BP also failed to modify the independent relationships between nurse office-day BP and target organ changes. Thus, the present study suggests that modifying

Table 4.5. Unadjusted (Pearson's r) and multivariate adjusted (Partial r) relationships between night systolic (SBP) or diastolic (DBP) blood pressure and target organ changes with and without adjustments for day BP.

	Adjustments*	Pearson's or Partial r	CI	p-values [†]
<u>Night SBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	0.30	0.22 to 0.38	<0.0001
	*+ Day SBP	0.05	-0.04 to 0.14	=0.46
Aortic PWV (n=662)	Unadjusted	0.45	0.38 to 0.50	<0.00001
	*+ Day SBP	0.09	0.01 to 0.17	<0.05
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	0.32	0.22 to 0.41	<0.0001
	*Day SBP	0.04	-0.07 to 0.14	=0.70
Aortic PWV (n=512)	Unadjusted	0.44	0.36 to 0.50	<0.0001
	*+ Day SBP	0.10	0.01 to 0.19	<0.05
<u>Night DBP vs</u>		<u>All participants</u>		
LVMI (n=463)	Unadjusted	0.25	0.16 to 0.33	<0.0001
	*+ Day DBP	0.08	-0.01 to 0.17	=0.16
Aortic PWV (n=662)	Unadjusted	0.38	0.31 to 0.44	<0.0001
	*+ Day DBP	0.06	-0.02 to 0.14	=0.11
		<u>Untreated participants</u>		
LVMI (n=356)	Unadjusted	0.26	0.16 to 0.36	<0.0001
	*+ Day DBP	0.06	-0.04 to 0.17	=0.50
Aortic PWV (n=512)	Unadjusted	0.44	0.37 to 0.51	<0.0001
	*+ Day DBP	0.08	-0.01 to 0.17	=0.06

LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants and hypertensives), regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only).

[†]Further adjusted for non-independence of family members.

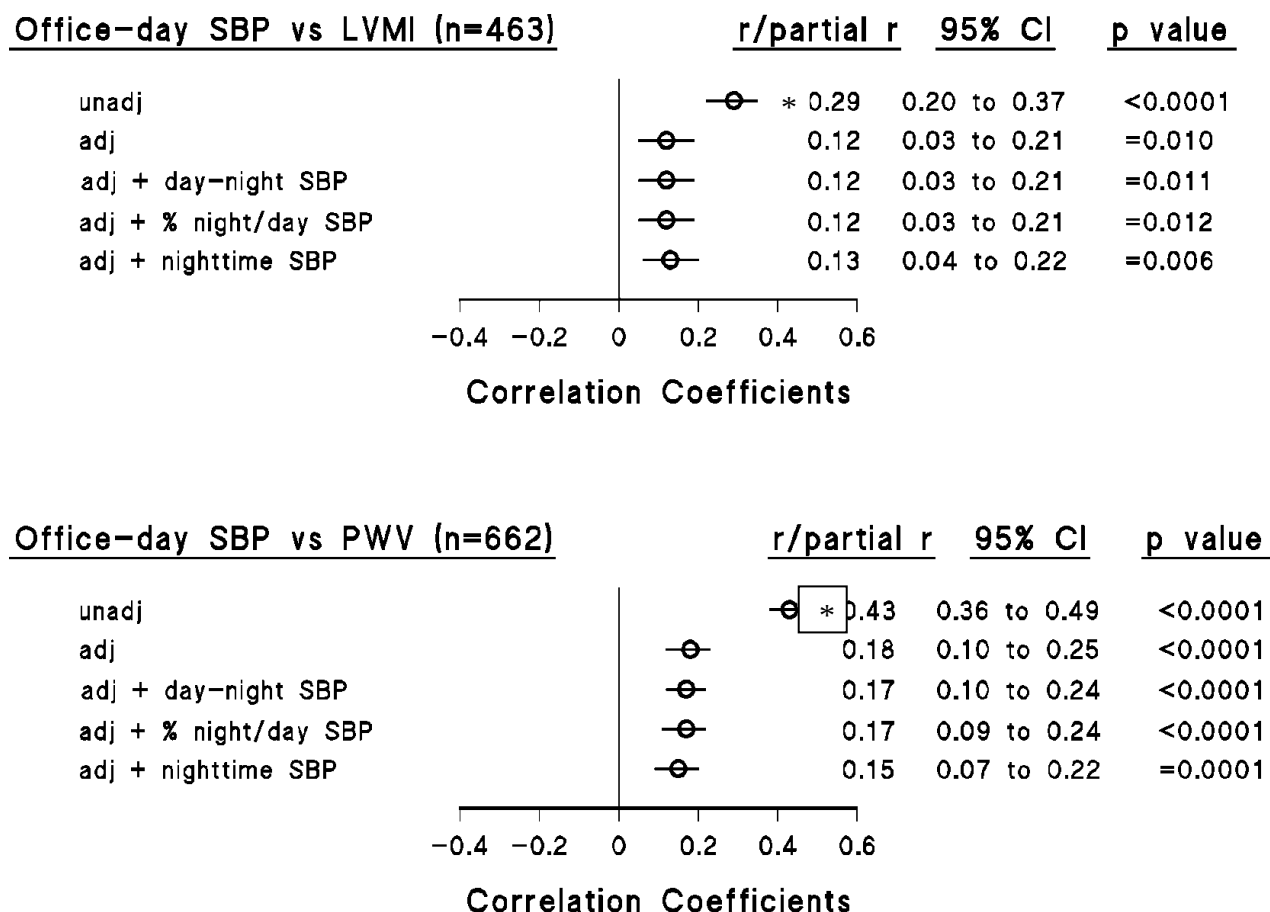


Figure 4.2. Independent relationships between nurse-elicited isolated increase in in-office BP (white-coat effect) as indexed by nurse office-day systolic blood pressure (SBP) and target organ changes before and after adjustment for nocturnal SBP dipping (day-night SBP or % night/day SBP) or nocturnal SBP and additional confounders. LVMI, left ventricular mass index; PWV, pulse wave velocity.*Adjustments are for age, sex, body weight (for LVMI), body mass index (for PWV), the presence of diabetes mellitus or HbA1c>6.1%, pulse rate, treatment for hypertension, regular tobacco use, regular alcohol intake and office mean arterial pressure (for PWV only). †Further adjusted for non-independence of family members.

the timing of antihypertensive therapy so that dosing is changed from morning to evening in order to ensure adequate decreases in nocturnal BP (chronotherapy) is unlikely to reduce the adverse effects of nurse-elicited white-coat responses.

Given that a reduced BP dipping and nocturnal BP has previously been demonstrated in a number of studies to have an adverse prognostic impact in several populations (O'Brien et al 1988, Zweiker et al 1994, Verdecchia et al 1994, 1998, 2000, 2007, 2012, Ohkubo et al 1997, 1998, 2002, Yamamoto et al 1998, Nakano et al 1998, 2004, Clement et al 2003, Sega et al 2005, Staessen et al 1999, Dolan et al 2005, 2009, Fagard et al 2004, 2005, 2008a, 2008b, 2009, Boggia et al 2007, Ingelsson et al 2006, Kario et al 2001, Ben-Dov et al 2007, Astrup et al 2007, Schwartz et al 2007, Brotman et al 2008, Ishikawa et al 2008, de la Sierra et al 2009, Fan et al 2010, Kikuya et al 2005, Palmas et al 2009, Ungar et al 2009, Bouhanick et al 2008, Dzielinska et al 2009, Muxfedt et al 2009, Mesquite-Bastos et al 2010) and is independently associated with target organ damage (Verdecchia et al 1990, Kuwajima et al 1992, Kawamoto et al 1991, Kario et al 1996), the question arises as to why neither indices of BP dipping nor night BP were associated with organ changes beyond 24-hour or day BP respectively in the present population? Importantly, the role of BP dipping as an independent predictor of cardiovascular outcomes is controversial. In 23 856 hypertensives and 9641 individuals from a variety of populations, dipping status, and the night/day ratio has previously been shown to add little prognostic information beyond 24-hour BP (Hansen et al 2011). Furthermore, in the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO), analysis conducted in 7458 individuals enrolled in population studies worldwide, although night BP was a better predictor of fatal endpoints than day BP and the night/day ratio predicted cardiovascular mortality, day BP was just as good as night BP for predicting combined fatal and non-fatal cardiovascular events and the night/day ratio lost its prognostic significance in untreated participants (Boggia et al 2007). In contrast, in 3012 never-treated hypertensives, a blunted or reverse dipping pattern was associated with cardiovascular outcomes independent of 24-hour BP and a number of confounders (Verdecchia et al 2012). Only intervention studies specifically targeting BP

dipping or nocturnal BP (lowering BP to nocturnal BP targets) will resolve the issue of the role of BP dipping and night BP beyond day BP in contributing toward adverse cardiovascular effects.

In the present and prior (Hansen et al 2011) studies, which have failed to show adverse effects of a blunted nocturnal dipping, the possibility that nocturnal BP obtained using brachial cuff measurements may not closely reflect actual night BP values must be considered. The possibility that the inability to decrease BP at night in some people may occur as a consequence of disturbed sleep patterns should be considered. In this regard, perceived sleep deprivation attenuates the relationship between nocturnal BP dipping and cardiovascular outcomes (Verdecchia et al 2007).

The results of the present study raise the question as to the possible mechanisms that may explain the relationship between nurse office-day BP (isolated increase in in-office BP or white coat-effect) and organ damage. The results of the present study suggest that BP at night is not involved in mediating these effects. Whether repeated BP surges during the course of a day, which may not be detected by BP measurements obtained every 15 minutes (the frequency of BP measurement), contribute toward the adverse effects indexed by the alerting response requires further study. Importantly, however, the results of the present study support prior studies that indicate that the impact of antihypertensive therapy on isolated increases in in-office BP are not associated with on-treatment reductions in target organ changes (Fagard et al 2000, Parati et al 2000). Nevertheless, whether office-day BP in these studies (Fagard et al 2000, Parati et al 2000) was limited as an index of the alerting response is uncertain. Hence, in chapter 5 I further explored whether antihypertensive therapy is able to diminish nurse-derived isolated increases in in-office BP (white-coat effects) and either whether this is indeed either associated with regression of left ventricular mass index or whether nurse-derived isolated increases in in-office BP predict an inability to regress increases in left ventricular mass index.

The limitations of the present study have been underscored in previous chapters and include the cross-sectional design which precludes conclusions being drawn regarding cause

and effect. Longitudinal studies and intervention studies specifically targeting isolated increases in in-office BP are therefore required. However, until the mechanism of this effect has been clearly identified and specific therapy targeting this mechanism has been developed, such a study will not be forthcoming. Second, the present study was conducted in one ethnic group, a group previously demonstrated to have a high prevalence of white-coat effects (Maseko et al 2011). Further studies with high quality in-office BP measurements conducted by a single nurse or technician-observer or with measurements well standardized across sites, are therefore required in alternative ethnic groups with a high prevalence of alerting responses to address this issue.

In conclusion, in the present study I show that although nurse-elicited isolated increases in in-office BP or white coat effects, as indexed by nurse office-day BP, are independently associated with an attenuated nocturnal BP decline, neither BP dipping nor night BP can explain the independent relationships between nurse-elicited isolated increases in in-office BP and target organ changes. These data suggest that modifying the time of taking antihypertensive therapy from morning to night dosing to ensure adequate decreases in nocturnal BP is unlikely to reduce the cardiovascular damage associated with nurse-elicited white-coat effects. Further studies are required to evaluate the mechanisms that explain the relationship between nurse-elicited isolated increases in in-office BP and cardiovascular damage.

CHAPTER 5

**Impact of Antihypertensive Therapy on Nurse Elicited Isolated
Increases in In-Office Blood Pressure in Hypertensives**

Abstract

Although nurse-elicited isolated increases in in-office blood pressure (BP), as indexed by nurse office-day BP are associated with target organ changes independent of ambulatory BP, whether nurse office-day BP is affected by antihypertensive therapy, is uncertain. In the present study the effect of antihypertensive therapy on nurse office-day BP was assessed in 173 patients whom, off treatment, had a daytime diastolic BP ranging from 90 to 114 mm Hg. Eligible patients were randomised to receive nifedipine gastrointestinal system at 30mg/day, verapamil slow release at 240 mg/day, hydrochlorothiazide at 12.5 mg/day, or enalapril at 10 mg/day and patients were followed up at monthly intervals for 4 months. At each monthly visit uptitration of therapy or the addition of therapy occurred. Antihypertensive drugs were titrated and combined to reduce the daytime diastolic BP below 90 mm Hg. Over the treatment period decreases in BP occurred in all treatment groups with the mean ($\pm$ SD) nurse office (baseline= $171\pm 20/102\pm 9$ mm Hg, 4 months= $148\pm 21/92\pm 11$ mm Hg, $p<0.0001$), mean day (baseline= $155\pm 14/101\pm 7$ mm Hg, 4 months= $133\pm 15/88\pm 9$ mm Hg, $p<0.0001$) and mean 24-hour (baseline= $150\pm 15/96\pm 7$ mm Hg, 4 months= $129\pm 14/83\pm 9$ mm Hg, $p<0.0001$) BP changing significantly from baseline. However, neither nurse office-day systolic (baseline= 16.5 ± 15.8 mm Hg, 4 months= 15.3 ± 18.9 mm Hg, $p=0.49$), nor diastolic (baseline= 0.9 ± 9.3 mm Hg, 4 months= 4.3 ± 10.7 mm Hg, $p<0.005$) BP decreased significantly from baseline. Class of antihypertensive agent initiated or added to initial therapy was not associated with changes in nurse office-day BP. In conclusion, even with the addition of second-line therapy, current recommended first-line therapy for the management of hypertension, despite producing marked decreases in nurse-derived in-office and out-of-office ambulatory BP, produces no significant change in nurse-elicited isolated increases in in-office BP (white coat-effects) in a group of African descent.

5.1 Introduction

Meta-analyses have demonstrated that an increased in-office, but normal out-of-office BP, often called white-coat or isolated in-office hypertension, predicts cardiovascular outcomes to a similar extent as that of sustained normotension (normal in and out-of-office BP) (Hansen et al 2007, Fagard et al 2007). However, alternative studies suggest a pathological role for isolated increases in in-office BP. Indeed isolated in-office hypertension has been associated with worse cardiovascular outcomes (Verdecchia et al 2005, Mancia et al 2006) and increased target organ changes (Kuwajima et al 1993, Glen et al 1996, Palatini et al 1997, Muscholl et al 1998, Owens et al 1998, Landray et al 1999, O'Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Sega et al 2001) as compared to normotensives in some studies, and in-office minus day BP, an index of isolated increases in in-office BP, is associated with target organ changes in hypertensives (Parati et al 1998, Maseko et al, chapter 3) and normotensives (Maseko et al, chapter 3). Nevertheless, whether the adverse effects of isolated increases in in-office BP reflect an impact of BP on cardiovascular target organs is uncertain.

If the potential adverse effects of isolated increases in in-office BP were attributed to the adverse effects of BP, then BP-lowering therapy should produce beneficial effects on cardiovascular damage in relationship to an attenuation of isolated increase in in-office BP. In this regard, one prior study has demonstrated that antihypertensive therapy given to hypertensives may decrease the difference between office and day BP, but that this difference is not associated with improvements in organ damage (Paratti et al 2000). In an alternative study, antihypertensive therapy given to elderly patients with isolated increases in in-office systolic BP reduced in-office, but not out-of-office BP, and these changes in in-office BP were not associated with improvements in target organ changes or cardiovascular outcomes (Fagard et al 2000,). However, neither of these studies specified whether physicians or nurses were employed to perform BP measurements (Paratti et al 2000, Fagard et al 2000). In this regard although nurses measure in-office BP values that are

higher than out-of-office values, the difference is nevertheless less evident than that of physicians (Little et al 2002). Despite the diminished increase in in-office BP in response to nurse-derived as compared to physician-derived BP measurement (Little et al 2002), nurse-derived isolated increases in in-office BP are nonetheless associated with target organ damage independent of ambulatory BP (Maseko et al, chapter 3). To further explore whether the association between nurse-elicited isolated increases in in-office BP and target organ changes are BP-related, I evaluated the impact of antihypertensive therapy on nurse office minus day BP and the possibility that nurse office-day BP predicts subsequent changes in left ventricular mass index.

5.2 Methods

5.2.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M940106). Participants gave informed, written consent. The study design has previously been described (Sareli et al 2001, Skudicky et al 2002). Hypertensives of black African descent 18-70 years of age, free of clinically significant cardiovascular and non-cardiovascular disease, were enrolled. Hypertension was diagnosed after a 2-week placebo run-in period, if daytime ambulatory diastolic blood pressure (BP) was 90-114 mm Hg.

Eligible patients were randomized to receive nifedipine gastrointestinal system (GITS) 30mg/d, verapamil slow release (SR) 240 mg/d, hydrochlorothiazide 12.5 mg/d or enalapril 10 mg/d and patients were followed up at monthly intervals for 4 months (Sareli et al 2001). At each monthly visit uptitration of therapy or the addition of therapy occurred as described (Sareli et al 2001). If target BP was not achieved (daytime diastolic BP < 90 mm Hg), at 1 month the daily dose of therapy was increased (nifedipine GITS, 60 mg, verapamil SR, 360

mg, hydrochlorothiazide 25 mg and enalapril 20 mg), and at 2 months in patients receiving nifedipine GITS, either enalapril 10 mg/d, carvedilol 25 mg/d, or verapamil SR were added or the dose of nifedipine GITS was increased to 90 mg/d. In patients receiving verapamil SR at 2 months the dose could be increased to 480 mg/d. In those receiving hydrochlorothiazide 25 mg/d, reserpine 0.125 mg/d could be added and in those receiving enalapril 20 mg/d, hydrochlorothiazide 12.5 mg/d could be added.

Of the 409 patients randomized in the trial, 233 (57%) were eligible for inclusion in the present substudy because echocardiograms of sufficient quality had been obtained. Of the latter patients, 23 (10%) had been withdrawn at 4 months and 37 (16%) did not have all measurements at baseline or at 4 months required for the statistical measurements. Thus, this study included 173 patients in total.

5.2.2 Blood pressure.

High quality conventional BP measurements were obtained by a trained nurse-technician according to guidelines (O'Brien et al 2003, Pickering et al 2005) using a standard mercury sphygmomanometer as previously described (Sareli et al 2001, Skudicky et al 2002). This approach was essentially the same as that described in chapter 2 (section 2.2.3). However, in the present study after the patient had rested in the sitting position for 10 minutes, the study nurse measured the conventional BP three times consecutively and the average was taken as the in-office BP.

At randomisation and at 4 months of therapy ambulatory 24-hour, day and night BP were determined using SpaceLabs monitors (model 90207) as previously described (Sareli et al 2001, Skudicky et al 2002). This approach was essentially the same as that described in chapter 2 (section 2.2.3). The analysis to obtain ambulatory 24-hour, day and night BP was also as described in chapter 2 (section 2.2.3). The average ($\pm$ SD) number of BP recordings obtained for the present study at baseline was 70.0 ± 9.6 (range=27-84) for the 24-hour period, 30.7 ± 5.4 (range=12-38) for the day and 16.9 ± 2.3 (range=6-19) for the night periods.

The average ($\pm$ SD) number of BP recordings obtained for the present study at 4 months was 68.5 ± 9.0 (range=42-82) for the 24-hour period, 30.5 ± 4.7 (range=14-38) for the day and 16.5 ± 3.0 (range=5-19) for the night periods.

5.2.3 Echocardiography

At randomization and at 4 months, M-mode, 2-dimensional, pulse and color Doppler echocardiograms were obtained with a Hewlett-Packard Sonos 2500 system using a 2.5-MHz transducer as described in chapter 3 (section 3.2.4.2). Briefly, M-mode echocardiography of the left ventricle was performed in the short-axis view. M-mode variables were analyzed according to the American Society of Echocardiography Convention (Sahn et al 1978) and included left ventricular end-diastolic and end-systolic diameters and septal and posterior wall thickness. All measurements were recorded on videotape and analyzed by the same experienced echocardiographer who was unaware of the BP and the clinic data of the patients. For statistical analysis, measurements were averaged over three heart cycles. Left ventricular mass (LVM) was calculated according to an anatomically validated method (Devereux et al 1986) given in chapter 3, section 3.2.4.2 and indexed to height^{2.7}. Replicate measurements of LVM index (LVMI) showed that in the present study population, the interobserver and intraobserver coefficients of variation were 12.4% and 11.4%, respectively.

5.2.4 Data analysis

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc). As in this study, relationships between changes in BP and changes in LVMI were previously reported in previously untreated participants (Skudicky et al 2002), in the present study analysis was also conducted in these separate groups. Previously untreated and treated patients were compared using Student's t test and the X^2 statistic for

continuous measurements and class variables, respectively. Single and stepwise multiple regression analyses were used to analyze the relationship between changes in LVM or LVM index and various explanatory variables, including the treatment-induced BP changes. Multivariate ANOVA was performed to test the null hypothesis of no differences between the parameters of regression equations. As the degree of hypertension may influence the extent of increment in nurse-day BP (chapters 2 and 3), when assessing the effects of antihypertensive therapy on nurse-day BP, sensitivity analysis was conducted in those with a 24-hour systolic BP<130 mm Hg.

5.3 Results

5.3.1 Patient characteristics

As compared with the 236 nonparticipants, the 173 participants had similar BP values at entry (Table 5.1). However, nonparticipants were older, more obese, and included slightly more previously treated patients (46% versus 37%, respectively, $p=0.052$). The 173 participants (41 men and 132 women) were 51 ± 10 years of age. Their body-mass index averaged 30.3 ± 6.2 kg/m². Of the 173 participants, 109 had previously been treated, and 85 patients had been on monotherapy either with diuretics ($n=48$), angiotensin-converting enzyme inhibitors ($n=20$), α -methyldopa ($n=9$), or calcium channel blockers ($n=8$). Furthermore, 17 patients had been on multiple drugs, including diuretics in 11 patients, and 7 patients could not report which drug treatment they had been taking before the screening visit. Compared with the untreated patients, the previously treated patients included more women and had higher mean body-mass index (Table 5.1). At entry, nurse and ambulatory BP values as well as nurse-day BP values (Table 5.2) as well as all echocardiographic measurements (Table 5.3) were similar in previously untreated and treated patients ($p>0.04$).

Table 5.1. Clinical characteristics at randomisation of participants and non-participants

	Non-participants	Participants		
		Previously Untreated	Previously Treated	All Included
Number	236	64	109	173
Age (years)	55±10	49±11	52±9	51±10*
Female sex, n (%)	181 (77)	40 (62.5)	92 (84.4) [‡]	132 (76)
BMI (kg/m ²)	31.8±7	28.4±6	31.4±6 [‡]	30.3±6.2 [‡]
<u>Systolic/Diastolic BP (mm Hg)</u>				
Nurse	173±18/103±7	170±17/103±9	172±21/102±9	172±21/102±9
24-Hour	150±15/96±7	149±15/96±7	153±15/97±7	153±15/97±7
Day	155±14/102±7	153±15/102±7	158±14/103±7	158±14/103±7
Night	139±18/85±10	140± 18/86±10	143±20/87±11	143±20/87±11
Nurse-Day	18.3±17.3/1.5±8.0	17.8±13.6/1.7±9.0	15.8±16.9/0.4±9.5	16.5±15.8/0.9±9.3

Values are mean±SD.*p<0.01 and [†]p=0.03, significance of the difference between participants and nonparticipants, [‡] p=0.002, significance of the difference between previously untreated and previously treated patients.

Table 5.2. Nurse-derived blood pressures (BP), ambulatory BP and nurse-day BP (an index of isolated increases in in-office BP) at baseline and at 4 months of antihypertensive therapy.

BP (mm Hg)	Baseline	4 Months	Change
<u>All participants (n=173)</u>			
Nurse	171±20/102±9	143±21/92±11	-23 ±26**/-10±14**
24-hour	150±15/96±7	129±14/83±9	-22 ±16**/-13±9**
Day	155±14/101±7	133±15/88±9	-23±18**/-14±11**
Night	145±17/90±9	125±16/77±9	-20±18**/-12±11**
Nurse-day	16.5±15.8/0.9±9.3	15.3±18.9/4.3±10.7	-1.3±22.7/3.4±13.5*
<u>Previously untreated (n=64)</u>			
Nurse	170±17/103±9	144±21/91±11	-24 ±25**/-12±14**
24-hour	148±14/96±7	126±14/81±8	-23 ±15**/-14±9**
Day	152±14/101±6	130±14/87±8	-24±17**/-15±10**
Night	143±16/90±9	122±16/76±9	-21±16**/-13±11**
Nurse-day	17.8±13.6/1.8±9.0	14.9±18.7/5.0±10.6	-2.9±21.0/3.3±12.3*
<u>Previously treated (n=109)</u>			
Nurse	172±21/102±9	150±22/93±11	-22±27**/-9±14**
24-hour	152±15/97±7	131±14/84±9	-21±17**/-13±10**
Day	156±14/102±7	134±15/89±10	-22±19**/-13±11**
Night	147±17/91±8	127±16/78±10	-19±18**/-12±12**
Nurse-day	15.8±16.9/0.4±9.5	15.5±19.2/3.8±10.7	-0.4±23.7/3.4±14.2*

*p<0.05, **p<0.001 for change in BP.

Table 5.3. Echocardiographic data at baseline and at 4 months of antihypertensive therapy.

Characteristic	Baseline	4 Months	Change	p-value
<u>All participants (n=173)</u>				
LVEDD (mm)	46.2±5.8	44.8±5.5	-1.4±6.0	<0.005
PWT (mm)	11.3±2.3	10.6±1.8	-0.8±2.2	<0.0001
IVS (mm)	12.3±2.2	11.4±1.9	-0.9±2.1	<0.0001
MWT (mm)	11.8±2.0	11.0±1.5	-0.8±1.8	<0.0001
LVM (g)	209±65	179±50	-30.7±49.9	<0.0001
LVMI (g/m ^{2.7})	60.3±18.4	51.5±13.6	-8.8±14.4	<0.0001
<u>Previously untreated (n=64)</u>				
LVEDD (mm)	47.0±4.9	46.4±4.6	-0.6±5.1	=0.34
PWT (mm)	11.1±2.1	10.3±1.7	-0.7±2.1	=0.007
IVS (mm)	11.9±2.3	11.0±1.7	-0.9±2.2	=0.003
MWT (mm)	11.5±2.1	10.7±1.4	-0.8±1.9	=0.001
LVM (g)	205±55	181±40	-24.4±42.9	<0.0001
LVMI (g/m ^{2.7})	58.7±19.3	51.4±14.1	-7.3±12.7	<0.0001
<u>Previously treated (n=109)</u>				
LVEDD (mm)	45.7±6.3	43.9±5.8	-1.8±6.4	=0.004
PWT (mm)	11.5±2.3	10.7±1.8	-0.8±2.3	<0.0005
IVS (mm)	12.6±2.0	11.6±1.9	-1.0±2.0	<0.0001
MWT (mm)	12.0±1.9	11.2±1.6	-0.9±1.8	<0.0001
LVM (g)	212±70	178±55	-33.7±52.6	<0.0001
LVMI (g/m ^{2.7})	61.3±17.8	51.6±13.4	-9.7±15.3	<0.0001

LVEDD: left ventricular end-diastolic diameter; PWT: end-distolic posterior wall thickness;
 IVS: end-diastolic interventricular septum thickness; MWT: end-diastolic mean wall thickness;
 LVM, left ventricular mass; LVMI, LVM index.

5.3.2 Relationships between nurse-day BP and day BP

At baseline, nurse-day systolic BP was not significantly related to day systolic BP ($r=-0.11$, $p=0.15$).

5.3.3 Antihypertensive therapy.

In the previously untreated participants the number of patients who remained on monotherapy was 27 of 39 in the nifedipine-treated group, 6 of 9 in the verapamil SR-treated group, 2 of 8 in the enalapril-treated group, and 4 of 8 in the hydrochlorothiazide-treated group. In the previously treated group, the number of patients that remained on monotherapy was 40 of 65 in the nifedipine-treated group, 14 of 17 in the verapamil SR-treated group, 3 of 14 in the enalapril-treated group, and 5 of 13 in the hydrochlorothiazide-treated arm. There were no significant differences in the use of study medications between previously untreated and treated patients ($p>0.42$).

5.3.4 Blood pressure reductions with antihypertensive therapy

In all participants as well as in those previously treated or previously untreated for hypertension, antihypertensive therapy produced a marked reduction in nurse-derived, 24-hour, day and night BP (Table 5.2). In the previously treated participants, the nurse-derived and ambulatory BP had fallen to the same extent as in the previously untreated group (Table 5.2). Despite a marked effect on absolute BP produced by antihypertensive therapy, the same therapy failed to modify nurse-day BP in either all participants, or in previously untreated or previously treated participants (Table 5.2). The inability to decrease nurse-day BP was noted across all treatment groups (data not shown). Moreover, antihypertensive therapy was unable to reduce nurse-day systolic BP in those participants with a baseline 24-hour systolic BP <130 mm Hg ($n=7$, Nurse-day systolic BP: Before; 13.6 ± 10.5 mm Hg; 4-

months 25.4 ± 13.2 mm Hg, $p=0.09$).

5.3.5 Effect of antihypertensive therapy on LVMI.

In previously untreated participants after 4 months of antihypertensive therapy, LVM and LVMI had decreased ($p<0.001$) by 24 g and 14 g/m^2 , respectively (Table 5.3). Similarly, in previously treated participants after 4 months of antihypertensive therapy with the study medications, LVM and LVMI had decreased by 34 g ($p<0.001$) and 19 g/m^2 ($p<0.001$), respectively (Table 5.3). In the previously untreated participants this was achieved through a reduction in wall thickness, but not left ventricular end-diastolic diameter (Table 5.3). In contrast, in the previously treated participants, the reduction in LVMI was achieved through a reduction in wall thickness and left ventricular end-diastolic diameter (Table 5.3). The reductions in all echocardiographic measurements were similar ($p>0.18$) in previously untreated and treated patients (Table 5.3).

5.3.6 Relationships between baseline BP or nurse-day BP values and baseline LVMI.

At baseline, nurse, 24-hour, day, night and nurse-day systolic BP (SBP) were all associated with LVMI in previously untreated participants, but not in previously treated participants (Table 5.4). The relationship between nurse-day SBP and LVMI was independent of either 24-hour (Table 5.4) or day (data not shown) SBP.

5.3.7 Relationships between treatment-induced changes in BP and LVMI

In previously untreated, but not in previously treated participants there was a positive linear relationship between the decrease in LVMI and the reduction in systolic BP as assessed by nurse-derived or by 24-hour ambulatory monitoring (Table 5.5). The corresponding relationship for diastolic pressure was not statistically significant (data not

Table 5.4. Multivariate adjusted correlation coefficients (partial r) between baseline systolic blood pressure or nurse-day SBP (an index of isolated increases in in-office BP or white-coat effects) and baseline left ventricular mass index (LVMI).

Baseline LVMI versus	Partial r	(CI)	p-value
<u>Previously untreated (n=64)</u>			
<u>Baseline systolic blood pressure</u>			
Nurse	0.40	(0.15 to 0.60)	<0.002
24-hour	0.35	(0.09 to 0.56)	<0.01
Day	0.31	(0.05 to 0.53)	<0.02
Night	0.36	(0.11 to 0.57)	<0.01
Nurse-day*	0.30	(0.04 to 0.52)	<0.05
<u>Previously treated (n=109)</u>			
<u>Baseline systolic blood pressure</u>			
Nurse	0.13	(-0.07 to 0.31)	=0.20
24-hour	0.09	(-0.11 to 0.28)	=0.38
Day	0.05	(-0.14 to 0.24)	=0.59
Night	0.11	(-0.09 to 0.30)	=0.27
Nurse-day*	0.12	(-0.08 to 0.31)	=0.24

All relationships are adjusted for age, sex, body weight, the presence of diabetes mellitus, regular tobacco use, and regular alcohol intake. *Further adjusted for 24-hour BP.

Table 5.5. Multivariate adjusted correlation coefficients for relationships between changes in (Δ) nurse or ambulatory systolic blood pressure (SBP) or nurse-day SBP (an index of isolated in-office increases in in-office BP or white-coat effects) and change in left ventricular mass index over 4 months of antihypertensive therapy.

Adjustments		Partial r	(95% CI)	p-value
<u>Previously untreated (n=64)</u>				
<u>Δ LVMI versus</u>				
Δ Nurse SBP		0.36	(0.13 to 0.57)	=0.003
Δ Nurse SBP	Δ 24-hour SBP	0.27	(0.03 to 0.49)	<0.05
Δ 24-hour SBP		0.28	(0.03 to 0.49)	<0.05
Δ Daytime SBP		0.13	(-0.12 to 0.36)	=0.32
Δ Nighttime SBP		0.30	(0.06 to 0.51)	<0.05
Δ Nurse-day SBP	Δ 24-hour SBP	0.28	(0.03 to 0.49)	<0.05
<u>Previously treated (n=109)</u>				
<u>Δ LVMI versus</u>				
Δ Nurse SBP		0.02	(-0.17 to 0.21)	=0.82
Δ Nurse SBP	Δ 24-hour SBP	0.07	(-0.12 to 0.26)	=0.47
Δ 24-hour SBP		-0.08	(-0.26 to 0.11)	=0.42
Δ Daytime SBP		-0.07	(-0.25 to 0.12)	=0.49
Δ Nighttime SBP		-0.05	(-0.23 to 0.14)	=0.63
Δ Nurse-day SBP	Δ 24-hour SBP	0.08	(-0.11 to 0.27)	=0.41

shown). The relationships between change in nurse-derived BP and change in LVMI persisted with adjustments for 24-hour BP (Table 5.5). The persistence of this relationship was attributed to a relationship between changes in nurse-day BP and changes in LVMI (Table 5.5).

5.4 Discussion

The main findings of the present study are as follows: Antihypertensive therapy given to those with hypertension as defined by increases in day diastolic BP values, despite producing a marked decrease in both nurse-derived in-office and ambulatory BP, failed to attenuate nurse-day BP, an index of nurse-elicited isolated increases in in-office BP (white-coat effects).

To the best of my knowledge, the present study is the first to assess whether isolated increases in in-office BP, or white-coat effects as elicited by nurses, may decrease with antihypertensive therapy. In contrast to the results of the present study, two prior studies conducted in elderly patients with isolated increases in in-office systolic BP (Fagard et al 2000) or in hypertensives (Parati et al 2000) suggest that antihypertensive therapy reduces in-office, but not out-of-office BP (Fagard et al 2000) or office-day BP (an index of isolated increases in in-office BP) (Parati et al 2000). However, whether nurses measured in-office BP in these studies was not specified (Fagard et al 2000, Parati et al 2000). In this regard although nurses measure in-office BP values that are higher than out-of-office values, the difference is nevertheless quantitatively less evident than that of physicians (Little et al 2002). Hence, isolated increases in in-office BP produced by nurses may not be the same as that produced by physicians and hence antihypertensive therapy may not mediate the same effects on isolated increases in in-office BP. However, the characteristic features of the population that I studied, such as of black African ancestry, with a high prevalence of obesity, and from an economically developing population, are largely different from that previously studied (Fagard et al 2000, Parati et al 2000) and these differences might also explain the

lack of effect of antihypertensive therapy on office-day BP despite marked effects on absolute BP.

In the present study the mean differences between nurse-day systolic BP noted at baseline and after 4 months of therapy in hypertensives (~18 mm Hg) was considerably higher than that reported on in the community-based study described in chapters 2-4 (~5 mm Hg). This apparent discrepancy is not however entirely inconsistent as white-coat hypertension was more evident in hypertensives irrespective of treatment (chapter 2) and treatment for hypertension was associated with increases in nurse office-day systolic BP (chapter 3). It does nevertheless raise the question as to whether antihypertensive therapy may better modify in-office rather than out-of-office increases in BP in subjects with otherwise normotensive ambulatory BP values. In this regard however, antihypertensive therapy failed to modify nurse-day BP even in those with a 24-hour systolic BP at baseline of <130 mm Hg.

The clinical importance of the present results warrant consideration. In this regard, as indicated in chapters 3 and 4, although nurse office-day BP values, an index of isolated increases in in-office BP (white-coat effects) are associated with target organ changes, and explain a significant proportion of nurse-derived BP-target organ relationships, these relationships are independent of ambulatory BP. These results therefore suggest that nurse-derived BP measurements should not be employed to make decisions regarding antihypertensive therapy. The present study provides further evidence to support this notion in that they show that nurse-elicited increases in in-office BP, as indexed by nurse office-day BP, cannot be modified by antihypertensive therapy.

The present analysis was designed to assess the effect of antihypertensive therapy on nurse-elicited isolated increases in in-office BP and the relationship of these changes with on-treatment regression of LVMI. As antihypertensive therapy failed to decrease nurse-elicited isolated increases in in-office BP, the relationship between these changes and on-treatment regression of LVMI could not be evaluated. Importantly, however, changes in nurse-day BP over the 4-month treatment period, changes which were not attributed to antihypertensive therapy, accounted for a significant proportion of the relationship between

changes in nurse BP and LVMI over time. Moreover, these relationships between change in nurse-day BP and change in LVMI were independent of 24-hour BP. Hence, the results of the present study provide longitudinal data to support the notion that the ambulatory BP-independent relationships between isolated increases in in-office BP elicited by nurses and target organ changes are indeed cause and effect. As these changes cannot be attributed to ambulatory BP, further work is required to determine the mechanism that explains these relationships.

The limitations of the present study include the fact that for ethical reasons, within various treatment groups, the impact of monotherapy alone on nurse-day BP could not be evaluated and the study was not placebo-controlled. Furthermore, this was an open label study and the study nurse and echocardiographer were aware that all patients were randomised to some form of antihypertensive therapy. However, these limitations would have been more important if I had noted that nurse-day BP was reduced by antihypertensive therapy. Last, I did not assess the effect of antihypertensive therapy on nurse-elicited isolated increases in in-office BP in those with normal ambulatory BP values only (white-coat hypertensives). However, antihypertensive therapy was unable to reduce systolic BP in those participants with a baseline 24-hour systolic BP < 130 mm Hg (n=7). Further work is nevertheless required in this regard.

In conclusion, the results of the present study indicate that despite marked reductions in absolute nurse and ambulatory BP, antihypertensive therapy is unable to reduce nurse office-day BP, an index of a nurse-elicited isolated increases in in-office BP, in hypertensives. Whether similar effects occur in those with white-coat hypertension (normal ambulatory, but elevated in-office BP) as identified from nurse-derived in-office BP measurement, requires further study.

CHAPTER 6

Summary and conclusions

In the present thesis I have extended our current knowledge and understanding of the value of nurse-derived in-office BP measurements for risk prediction in urban, developing communities of African ancestry in South Africa. In this regard, as summarised in chapter 1, although 24-hour ambulatory BP measurements are currently considered the ideal BP measurement, the cost of monitors for these measurements precludes their use for routine care, at least in the public healthcare sector. However, in South Africa in the public health sector, primary prevention of cardiovascular disease for the majority of South Africans is provided by nurses rather than physicians. In this regard, it is now well-recognised that nurses record auscultatory BP with fewer errors, with lower values than physicians and with less of an alerting response than physicians (Veerman et al 1993, Graves et al 2004, Pickering et al 2005, Little et al 2002). Moreover, nurse-derived values are often as closely associated with organ damage as out-of-office ambulatory BP (Nystrom et al 2005, Veerman et al 1996, de Blok et al 1991, Jula et al 1999, Moran et al 2006, Woodiwiss et al 2009). Thus, for some years, nurse-derived BP measurements have been perceived as a better method of risk-predicting than alternative methods of in-office BP measurements. However, although nurse-derived BP measurements may be a more appropriate method of in-office BP measurement than alternative in-office BP measurements, a number of questions remain with regards to the validity of these measurements as compared to 24-hour BP measurements. These questions have largely been addressed in the current thesis. In the present chapter I will summarise the findings of the present thesis in the context of our existing understanding of the role of in-office versus ambulatory BP measurement for risk association.

6.1 “White-coat” effects are highly prevalent with nurse-derived in-office BP measurement.

Although there has been important data previously published to show that nurses measure BP with significantly lower values than physicians and with less of an alerting

response (Little et al 2002), there is nevertheless no question that an alerting response does occur irrespective of who measures the BP (nurse or physician). Indeed, in the present thesis the mean difference between in-office systolic BP measured by a single nurse and day BP in the 750 participants from a community-based sample was 5.8 ± 15.4 mm Hg. This value is indeed in-keeping with previously reported values in alternative publications (Little et al 2002) which although markedly lower than physicians, still represents a mean in-office systolic BP that is higher than day systolic BP despite being measured at rest, while day systolic BP is measured during normal daily activities. Despite these relatively minor mean differences in nurse-derived in-office systolic BP and day systolic BP determined using ambulatory BP measurements, as indicated in chapter 2 of the present thesis, there were sufficient participants with higher in-office BP measurements for this to translate into a markedly higher prevalence of uncontrolled in-office BP (37.2%) as compared to uncontrolled ambulatory BP (24.1%) ($p < 0.0001$). These differences in the assessment of BP control evaluated with nurse-derived as compared to ambulatory BP occurred despite the fact that more participants had uncontrolled BP at night (34.0%) than during the day (22.6%, $p < 0.0001$). Moreover, these differences in uncontrolled nurse-derived as opposed to ambulatory BP were noted across a number of subgroups including women (35.1 vs 22.3%), men (40.8 vs 27.4%), obese (48.4 vs 29.8), non-obese (29.7 vs 20.3%), smokers (40.4 vs 31.3), and non-smokers (36.6 vs 22.9%). What are the implications of these findings for the management of hypertension in the public health sector in South Africa?

The marked underestimation of BP control using nurse-derived BP measurements suggests that in urban, developing communities of African descent, even under the best conditions and with high quality BP measurements, nurse-derived conventional BP measurements may result in the treatment of a significant number of people who are not at risk for the adverse effects of BP because they have white-coat effects. Importantly, marked differences in the proportion of either untreated or treated hypertensive participants with uncontrolled nurse-derived BP and ambulatory BP were noted (all: CBP=81.3%, ABP=44.4%, $p < 0.0001$; treated: CBP=62.2%, ABP=33.3%, $p < 0.0001$). Thus, in addition to

inappropriately initiating therapy in previously untreated individuals whose risk for BP-related cardiovascular events does not warrant therapy, it is also possible that a significant number of previously treated patients will either have therapy uptitrated or additional therapy added when this is not required. These potentially inappropriate actions may occur in 16.9% of the community, with obvious major cost implications to the health care system and possible adverse effects (side-effects) outweighing the benefits of BP reduction. There are nevertheless caveats to these arguments which need to be considered. What are these caveats?

Of those participants who I have identified as being at risk of receiving inappropriate therapy, a significant portion of these may require additional therapy to achieve lower BP targets because of their global risk profiles (the community has a high prevalence of diabetes mellitus or an HbA1c>6.1%). However, in these cases I also assume that the ambulatory BP targets should be proportionately lower. Nevertheless, as white-coat hypertension is associated with a lack of nocturnal BP dipping (Bochud et al 2009), a recognised risk factor for cardiovascular damage, it is possible that a proportion of participants with white-coat effects may ultimately develop cardiovascular damage and hence may benefit from the initiation of or addition of further antihypertensive therapy to adequately reduce night BP values, or to modify their treatment regimens to take morning doses at night (chronotherapy). Moreover, there is still considerable debate as to whether “white-coat” effects are in fact of pathophysiological significance and hence whether white-coat hypertension warrants therapy. As a consequence of these uncertainties, in the present thesis I further evaluated the potential pathophysiological role of “white-coat” effects, as elicited by nurses. What were these findings and what are the potential implications for the management of hypertension?

6.2 Potential pathophysiological role of nurse-elicited “white-coat” effects.

In the present thesis I subsequently evaluated whether the difference between nurse-derived in-office BP measurements and day BP, an index of nurse-elicited “white-coat”

effects are associated with indices of end-organ damage and whether these effects are dependent or independent of ambulatory BP. In this regard, a number of studies have demonstrated that “white-coat” hypertension is associated with cardiovascular outcomes or end-organ damage (Verdecchia et al 2005, Mancia et al 2006, Kuwajima et al 1993, Glen et al 1996, Palatini et al 1997, Muscholl et al 1998, Owens et al 1998, Palatini et al 1998, Landray et al 1999, O’Leary et al 1999, Zakopoulos et al 1999, Muldoon et al 2000, Segal et al 2001), but these effects have been attributed to the higher ambulatory BP values that are often noted in those with “white-coat” hypertension than those without (Fagard et al 2007, Mancia et al 2006). Furthermore, “white-coat” responses, as assessed from office minus day BP, are strongly associated with organ damage, but this effect has only been reported to occur at higher (hypertensive) BP values (Palatini et al 1997) and office-day BP in that study was inversely associated with day BP (Palatini et al 1997) a relationship which casts doubt on the value of this index as a “white-coat” response (Parati et al 1998). In the present study were nurse-derived in-office BP values associated with end organ damage and if so were these relationships dependent on ambulatory BP; only present at higher ambulatory BP values; and they were a reflection of an inverse relationship with day BP?

In the present thesis I show that despite the small mean difference between nurse-derived in-office systolic BP and ambulatory day systolic BP, the difference between these BP values was not a reflection of an inverse association with day systolic BP; was associated with end-organ damage (LV mass index and aortic PWV) across quartiles independent of all confounders and either 24-hour or day BP; and was noted in both those with a normal day BP and in hypertensives. Thus, the results of the present thesis provide the first evidence to show that the alerting response elicited by nurse-derived in-office BP measurement, despite showing a low average in-office increase in BP, has strong pathophysiological relevance, but that this effect may not be attributed to BP effects *per se*. Importantly, these findings provide an explanation for the strength of the relationships between nurse-derived BP measurements and end organ damage, often shown to be as strongly associated with end-organ damage as ambulatory BP (Nystrom et al 2005, Veerman et al 1996, de Blok et al 1991, Julia et al 1999,

Moran et al 2006, Woodiwiss et al 2009). In this regard, nurse-derived BP measurements index cardiovascular damage not only attributed to BP effects, but also attributed to an effect that cannot be accounted for by 24-hour BP measurements. These findings suggest that treating BP *per se* may have little impact on the adverse effects indexed by nurse-elicited “white-coat” effects.

However, as “white-coat” effects are associated with a lack of nocturnal BP dipping (Bochud et al 2009), a recognised risk factor for cardiovascular damage, and as demonstrated in chapter 2, night BP values showed worse control than day BP values in the community studied, it is possible that a proportion of participants with nurse-elicited “white-coat” effects may ultimately develop cardiovascular damage and hence may benefit from the initiation of or addition of further antihypertensive therapy designed to target nocturnal BP. In this regard, an attenuated nocturnal BP at night can be modified using the principles of chronotherapy, where antihypertensives are given in the evening rather than in the day. As most antihypertensives exert stronger BP lowering effects over the first as compared to the second 12 hours, generally, their impact on nocturnal BP values, is less than that on day BP. As a consequence of the possibility that the pathophysiological relevance of “white-coat” effects may be through an impact on an attenuated nocturnal decline in BP, in the present thesis I subsequently evaluated whether nurse-derived “white-coat” effects are associated with an attenuated decline in BP at night and whether this relationship may explain the association between nurse-elicited “white-coat” effects and end organ damage. What were these findings and what are the potential implications for the management of hypertension?

6.3 Does an attenuated nocturnal BP explain the pathophysiological role of nurse-elicited “white-coat” effects.

In the present thesis I provide strong evidence to confirm previous findings (Bochud et al 2009) that “white-coat” effects are indeed independently associated with an attenuation of nocturnal decreases in BP, as indexed by day-night and % night/day BP. The present

study nevertheless extends this study finding (Bochud et al 2009) by showing that this relationship exists between nurse-elicited “white-coat” effects and indices of nocturnal decreases in BP and that an attenuated nocturnal decrease in BP cannot explain the strong independent relationships between nurse-elicited “white-coat” effects and end organ damage. These data therefore provide evidence to suggest that modifying nocturnal BP by employing chronotherapy, is unlikely to attenuate the adverse impact of nurse-elicited “white-coat” effects on end-organ damage. These data therefore provide further evidence to suggest that the adverse effects of nurse-elicited “white-coat” responses are not attributed to BP *per se*.

Importantly, the results of the present study raise the question of the relative importance of an attenuated nocturnal decrease in BP noted in groups of African ancestry. In this regard, as demonstrated in a meta-analysis and a large community-based study, in groups of African ancestry out-of-office ambulatory BP values may be higher than other populations for a given level of in-office BP because of attenuated decreases in BP at night (Profant and Dimsdale 1999, Wang et al 2006). Moreover, these differences have been confirmed in the Dietary Approaches to Stop Hypertension (DASH) study (Jehn et al 2008). In the present thesis the higher prevalence of uncontrolled nocturnal as compared to day BP in hypertensives irrespective of whether they were receiving antihypertensive therapy provides additional evidence to suggest that this population group is particularly susceptible to an inability to decrease BP at night. Given that a reduced BP dipping and nocturnal BP has previously been demonstrated in a number of studies to have an adverse prognostic impact in several populations (O’Brien et al 1988, Zweiker et al 1994, Verdecchia et al 1994, 1998, 2000, 2007, 2012, Ohkubo et al 1997, 1998, 2002, Yamamoto et al 1998, Nakano et al 1998, 2004, Clement et al 2003, Segal et al 2005, Staessen et al 1999, Dolan et al 2005, 2009, Fagard et al 2004, 2005, 2008a, 2008b, 2009, Boggia et al 2007, Ingelsson et al 2006, Kario et al 2001, Ben-Dov et al 2007, Astrup et al 2007, Schwartz et al 2007, Brotman et al 2008, Ishikawa et al 2008, de la Sierra et al 2009, Fan et al 2010, Kikuya et al 2005, Palmas et al 2009, Ungar et al 2009, Bouhanick et al 2008, Dzielinska et al 2009, Muxfeldt et al

2009, Mesquite-Bastos et al 2010) and is independently associated with target organ damage (Verdecchia et al 1990, Kuwajima et al 1992, Kawamoto et al 1991, Kario et al 1996), the question arises as to why neither indices of BP dipping nor night BP were associated with organ changes beyond 24-hour or day BP respectively in the present population? What could the potential explanations for this apparent conundrum be?

Importantly, the role of BP dipping as an independent predictor of cardiovascular outcomes is not entirely clear. As previously discussed in chapters 1 and 4, in 23 856 hypertensives and 9641 individuals from a variety of populations, dipping status, and the night/day ratio has previously been shown to add little prognostic information beyond 24-hour BP (Hansen et al 2011). Furthermore, in the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO), analysis conducted in 7458 individuals enrolled in population studies worldwide, although night BP was a better predictor of fatal endpoints than day BP and the night/day ratio predicted cardiovascular mortality, day BP was just as good as night BP for predicting combined fatal and non-fatal cardiovascular events and the night/day ratio lost its prognostic significance in untreated participants (Boggia et al 2007). In contrast, in 3012 never-treated hypertensives, a blunted or reverse dipping pattern was associated with cardiovascular outcomes independent of 24-hour BP and a number of confounders (Verdecchia et al 2012). Only intervention studies specifically targeting BP dipping or nocturnal BP will resolve the issue of the role of BP dipping and night BP beyond day BP in contributing toward adverse cardiovascular effects.

It is nevertheless also important to consider that in the present and prior (Hansen et al 2011) studies, which have failed to show adverse effects of a blunted nocturnal dipping, the possibility that nocturnal BP obtained using brachial cuff measurements may not closely reflect actual night BP values must be considered. The possibility that the inability to decrease BP at night in some people may occur as a consequence of disturbed sleep patterns should be considered. Indeed, perceived sleep deprivation attenuates the relationship between nocturnal BP dipping and cardiovascular outcomes (Verdecchia et al 2007). In the present study I did not assess the extent of perceived sleep deprivation.

6.4 Can antihypertensive therapy attenuate nurse-elicited “white-coat” effects?

Although as discussed in aforementioned sections, the relationships between nurse-elicited “white-coat” effects and end-organ damage noted in the community sample studied were independent of ambulatory BP and attenuated nocturnal decreases in BP, one cannot exclude the possibility that antihypertensive therapy may reduce the difference between in-office and day BP and consequently produce beneficial effects on organ damage. Indeed, two studies have demonstrated that antihypertensive therapy may either decrease the difference between in-office and day BP (Paratti et al 2000), or decrease in-office, but not out-of-office BP (Fagard et al 2000). However, in neither of these studies were the effects of antihypertensive therapy on in-office BP associated with beneficial effects on end-organ damage (Paratti et al 2000, Fagard et al 2000). Nevertheless, neither of these studies specified whether physicians or nurses were employed to perform BP measurements (Paratti et al 2000, Fagard et al 2000). Hence, in the present thesis I also evaluated whether antihypertensive therapy could modify nurse-elicited “white-coat” responses as indexed by in-office-day BP, and if so whether this translates into a relationship with on-treatment changes in LV mass index. Importantly, in this study which is described in chapter 5. baseline nurse-day systolic BP was associated with LV mass index in previously untreated participants and this relationship was independent of either 24-hour or day systolic BP. These data obtained in hypertensives therefore corroborate the findings reported in the community-based sample in chapter 3. The fact that these relationships only occurred in the previously untreated participants, but not in the previously treated participants was not surprising, as neither in-office, nor ambulatory BP were associated with LV mass index in the previously treated hypertensives. What was the impact of antihypertensive therapy on in-office-day BP?

Despite marked mean differences in nurse-derived in-office systolic BP and day systolic BP in hypertensives at baseline (16.5 ± 15.8 mm Hg), and a significant reduction in systolic BP produced by antihypertensive therapy over a 4 month treatment period (mean decrease in 24-hour systolic BP = 22 ± 16 mm Hg), antihypertensive therapy failed to

significantly modify the difference between nurse-derived in-office systolic BP and day systolic BP (-1.3 ± 22.7 mm Hg). Thus, in contrast to previous findings where antihypertensive therapy decreased the difference between in-office and day BP, in the present study this difference, as elicited by nurse-derived in-office BP measurements, was not affected by antihypertensive therapy. Importantly, however, I evaluated the effect of antihypertensive therapy on nurse-derived in-office-day BP in patients with ambulatory day diastolic BP measurements >90 mm Hg. I did not assess the effect of antihypertensive therapy on nurse-derived in-office-day BP in “white-coat” hypertensives. Nevertheless, antihypertensive therapy was also unable to reduce systolic BP in those participants with a baseline 24-hour systolic BP <130 mm Hg ($n=7$).

As antihypertensive therapy failed to reduce the difference between nurse-derived in-office BP and day BP, in the present thesis I was unable to evaluate whether on-treatment reductions in nurse-derived in-office BP and day BP were independently associated with on-treatment decreases in LV mass index. However, changes in nurse-day BP over the 4-month treatment period accounted for a significant proportion of the relationship between changes in nurse BP and LVMI over time. Moreover, these relationships between change in nurse-day BP and change in LVMI were independent of 24-hour BP. Hence, the results of the present study provide longitudinal data to support the notion the ambulatory BP-independent relationships between isolated increases in in-office BP elicited by nurses and target organ changes represent cause and effect.

The implications of the findings that nurse-elicited “white-coat” effects cannot be modified by antihypertensive therapy require consideration. As indicated in chapters 3 and 4, the relationships between nurse-elicited “white-coat” effects and end-organ damage were noted to be independent of 24-hour, day or night BP and of an attenuated nocturnal decrease in BP. These findings suggested that although nurse-derived BP measurements, which encompass the adverse effects of nurse-elicited “white-coat” responses, may be useful for overall risk-prediction, that the relationships between these measurements and cardiovascular damage are likely to incorporate an effect which cannot be attributed to the

actions of BP *per se*. In this regard, the inability of antihypertensive therapy to reduce the nurse-elicited “white-coat” response confirms this notion.

6.5 Limitations of the present thesis and future studies

As with any study, the present thesis has certain limitations. Many of these limitations have already been acknowledged in each of chapters 2-5. However, some limitations are worthy of repetition and some important limitations of the thesis in general have not been discussed. First, as with the field of ambulatory BP monitoring in general, I did not compare the effect of antihypertensive therapy on organ damage when targeting nurse as compared to ambulatory BP. This study would have provided more convincing evidence that the use of antihypertensive therapy should be based on ambulatory rather than in-office BP. However, until ambulatory BP targets are accepted by guidelines for the management of hypertension, this study would not be ethical. Second, I did not perform a study to evaluate the impact of modifying antihypertensive therapy in order to achieve better night as compared to day BP control on end-organ damage. Again, until guidelines recommend such an approach, this study would not have been ethical. Third, I assessed the relationships between nurse-elicited “white-coat” effects and organ damage in a cross-sectional study design. In this regard, no conclusions can be drawn regarding cause and effect. I attempted in-part to rectify this problem by assessing the impact of on-treatment decreases in nurse-elicited “white-coat” effects and decreases in LV mass index. However, as antihypertensive therapy failed to modify nurse-elicited “white-coat” effects I could not address this question even with an intervention study. Until I am able to identify an approach which eliminates nurse-elicited “white-coat” responses or I am able to target the cause of these changes, this question cannot be answered. Fourth, I failed to identify the mechanism that could explain the ambulatory BP-independent relationship between nurse-elicited “white-coat” effects and end-organ damage. In this regard, it is possible that sympathetic activation may explain these relationships and hence that antihypertensive therapy targeting the sympathetic nervous

system should be evaluated. Lastly, as the majority of participants in these studies were women, it is possible that the results may pertain to women only. Nevertheless, in subgroup analyses in chapter 2, I showed that the proportion of participants with uncontrolled CBP was similar in men compared to women.

6.6 Conclusions

In conclusion, the results of the present thesis indicate that in an urban, developing community of African descent, as compared to 24-hour BP measurements, nurse-derived BP measurements elicit a significant in-office increase in BP which translates into a marked underestimation of BP control at a community level; is strongly associated with organ damage through effects that cannot be attributed to 24-hour BP or to relationships with an attenuated decline in nocturnal BP; and which cannot be treated with antihypertensive therapy. Further work is therefore required to assess the most cost-effective approach to excluding nurse-elicited isolated increases in in-office BP e.g by using cheap ABP monitors before initiating antihypertensive therapy to groups of African descent.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Woodiwiss/Norton

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M070469

PROJECT

Gene Candidates As Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black S Africans

INVESTIGATORS

Profs A/G Woodiwiss/Norton

DEPARTMENT

School of Physiology

DATE CONSIDERED

07.05.09

DECISION OF THE COMMITTEE*

Approved unconditionally (refer M020472)

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.05.09

CHAIRPERSON



(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Woodiwiss A Prof

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)

Ref: R14/49 Woodiwiss/Norton et al

CLEARANCE CERTIFICATE

PROTOCOL NUMBER M02-04-72

PROJECT

Gene Candidates As Determinants of Blood Pressure And Intermediary Phenotypes In Pathogenesis of Hypertension In Black South Africans

INVESTIGATORS

Prof's AJ/G et al Woodiwiss/Norton et al

DEPARTMENT

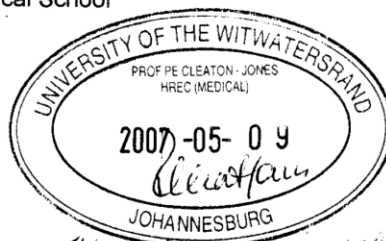
School of Physiology, Wits Medical School

DATE CONSIDERED

02-04-26

DECISION OF THE COMMITTEE *

Approved unconditionally



This clearance is valid and within the 16th 5-year validity.

DATE 02-05-14

CHAIRMAN

(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Prof AJ Woodiwiss

Dept of School of Physiology, Wits Medical School

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Prof A/G Woodiwiss/Norton

CLEARANCE CERTIFICATE

M1204108

PROJECT

Gene Candidates as Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black South

Africans (Previously M020472 and M070469)

INVESTIGATORS

Prof A/G Woodiwiss/Norton.

DEPARTMENT

School of Physiology

DATE CONSIDERED

Ad hoc

DECISION OF THE COMMITTEE*

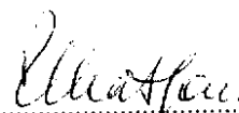
Renewal Approved

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE

2012/05/18

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof A Woodiwiss

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...