Blood Pressure Measurement Anno 2016

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The rational management of hypertension (HT) inevitably starts with accurate measurement of blood pressure (BP). The recently published Systolic Blood Pressure Intervention Trial implemented automated office BP measurement. However, event-driven studies have overwhelmingly indicated that out-of-the-office BP monitoring is a prerequisite for risk stratification and for identifying the need of initiating or adjusting antihypertensive drug treatment. 24-Hour ambulatory BP monitoring is the preferred method of BP measurement and addresses major issues not covered by conventional or automated office BP measurement or home BP monitoring, such as reliably diagnosing nocturnal HT (the time window of the day during which BP is most predictive of adverse cardiovascular outcome), hypotension, or masked HT, a condition that affects 15% of the general populations and carries a risk equal to that of HT on both office and out-of-the-office BP measurement. Moreover, 24-hour ambulatory BP monitoring is cost-effective. Outcome-driven criteria support single BP thresholds that can be applied in both sexes and across the age range. In conclusion, the overall evidence now overwhelmingly shows that ambulatory BP monitoring is mandatory for the proper management of HT. Health care providers should therefore facilitate access to this technique in both primary and specialized care.

Keywords: ambulatory blood pressure monitoring; blood pressure; home blood pressure recording; hypertension; office blood pressure measurement.

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The time has come to revise the approach to the management of hypertension. Using current strategies, clinicians have failed to stop what has been dubbed the "the largest epidemic ever known to mankind."[1] Indeed, at all ages, high blood pressure is the major driver of cardiovascular complications.[2] The Global Burden of Diseases Study 2010 reported that high blood pressure is the leading risk factor for ill health and causes 9.4 million deaths every year—more than half of the estimated 17 million deaths per year attributable to total cardiovascular disease.[3,4] The US Preventive Services Task Force,[5] the UK National Institute for Health and Clinical Excellence,[6] the European Society of Hypertension,[7] and the Canadian Hypertension Education Program[8] carefully examined the evidence as to which method of blood pressure measurement is best. All have each emphatically recommended ambulatory blood pressure monitoring as the method of choice. This review summarizes the evidence.

TECHNIQUES OF BLOOD PRESSURE MEASUREMENT

The rational and cost-effective management of hypertension rests on the accurate and reproducible diagnosis of the blood pressure level. In this section, we will shortly discuss, the methods available to clinicians to measure blood pressure.

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Office blood pressure measurement

Traditionally, office blood pressure measurement has been performed using a sphygmomanometer and stethoscope. However, because mercury as a toxic metal is being phased out and because properly validated oscillometric devices are readily available, the auscultatory technique is increasingly being replaced by automated techniques. An alternative to the mercury sphygmomanometer is the so-called "hybrid" sphygmomanometer, which combines features of electronic and mercury devices. It uses an electronic pressure gauge as a substitute for the mercury column. Blood pressure is taken in the same way as with a mercury device, using a stethoscope and listening for the Korotkoff sounds. The cuff pressure is displayed as a simulated mercury column, using an array of light emitting diodes or as a digital display.[9]

Factors that introduce inaccuracy in office blood pressure measurement originate in the patients, for instance as a consequence of inadequate posture or arousal, in the blood pressure measuring device, for instance because of improper validation of the device being used, or in the application of the technique. However, for the auscultatory approach, the observer is the main source of error.[9] Terminal digit preference refers to the observer rounding off the blood pressure reading to a digit of her or his choosing, most often 5 or zero.[10] Number preference refers to the number of identical blood pressure readings made by an observer within and between patients.[10] Nevertheless, doctors should maintain the skills to measure blood pressure using the auscultatory approach, because automated oscillometric devices may be inaccurate in patients with atrial fibrillation, tachycardia, or arrhythmia.[11,12] Hypertension on conventional office blood pressure measurement are levels of 140 mm Hg systolic or 90 mm Hg diastolic or higher. A further subdivision of office blood pressure levels as proposed by the European Society of Cardiology/European Society of Hypertension 2013 guidelines are shown in Table 1.[13]

Automated office blood pressure measurement

Automated office blood pressure is the average of multiple blood pressure readings recorded with a fully automated device with the patient resting silently, alone, in a quiet room of the office or clinic.[14] Compared with the conventional office blood pressure, automated office blood pressure, minimizes the office-induced increase in blood pressure, improves accuracy, reduces observer error, and provides a more standardized measurement technique by the use of an automated oscillometric sphygmomanometer.[15] Preliminary data suggest that automated office blood pressure is a better predictor of target organ damage,[16,17] especially compared with routine manual office blood pressure, which correlates poorly with intermediate endpoints, such as left ventricular mass.[17] In 2015, Myers *et al.* reported that in 3,627 older community-dwelling residents cardiovascular risk significantly increased at an automated office systolic blood pressure of 135 to 144 mm Hg and at a diastolic blood pressure of 80 to 89 mm Hg.[18] The Canadian Hypertension Education Program[8] has recommended automated office blood pressure measurement as the preferred method for assessing the office blood pressure.

In the recently published Systolic Blood Pressure Intervention Trial (SPRINT),[19] blood pressure was measured in the office with automated devices, unattended, after a 5-minute resting period. Three consecutive readings were averaged. SPRINT was the first hypertension trial implementing automated office blood pressure measurement and by doing so stirred a debate, which level of the conventional in-office blood pressure would be equivalent to the systolic targets in this trial of 120 mm Hg and 140 mm Hg, respectively. Some experts proposed that these levels would correspond with a conventional in-office systolic blood pressure approximately 10 mm Hg higher.[20,21] According to current European guidelines,[13] the automated office blood pressure thresholds for diagnosing hypertension are similar to those for the mean awake ambulatory and home blood pressures (135/85 mm Hg; Table 1).

Table 1. Systolic and diastolic blood pressure thresholds for blood pressure

Office blood pressure			Out-of-the-office blood pressure		
Conventional		Automated	Ambulatory		Home
Normotension	<140 and < 90	<135 and <85	Daytime	<135 and <85	<135 and <85
Optimal	<120 and <80		Nighttime	<120 and <70	
Normal	120–129 or 80–84		24 hours	<130 and <80	
High-normal	130–139 or 85–89				
Hypertension	≥140 or ≥90	≥135 or ≥85	Daytime	≥135 or ≥85	≥135 or ≥85
Grade I (mild)	140–159 or 90–99		Nighttime	≥120 or ≥70	
Grade II (moderate)	160–179 or 100–109		24 hours	≥130 or ≥80	
Grade III (severe)	≥180 or ≥110				
Isolated systolic hypertension	≥140 and <90				

Blood pressure thresholds are given in mm Hg. Consensus classification proposed by the 2013 European guidelines.[13]

24-Hour ambulatory blood pressure monitoring

Over the past 30 years, ambulatory blood pressure monitoring developed into the state-of-the-art technique for blood pressure measurement. Ambulatory monitoring substantially refines the risk stratification provided by office blood pressure both in hypertensive patients[22–24] and in the general population.[25–28] The greater number of readings, the absence of digit preference and observer bias, and the reduction of the white-coat effect all contribute to the predictive superiority of ambulatory over office blood pressure.[7] Patients undergoing ambulatory blood pressure monitoring should keep a diary providing information on the awake and asleep periods, the intake of medications, the timing of meals and physical exercise, and symptoms, if any. Short-fixed clock-time intervals that eliminate the transition periods in the morning and evening, during which blood pressure changes rapidly produce daytime and nighttime blood pressure levels, which are within 1 to 2 mm Hg of the awake and asleep levels.[29,30] Technological advances now allow devices for ambulatory blood pressure monitoring to indicate body position and activity, features that further enhance the relevance of the recorded blood pressure. Innovative digital technologies are moving towards a cuff-less approach to ambulatory blood pressure monitoring, thereby increasing patient comfort.[31] However, none of these devices has been proven to generate data that predict adverse health outcomes or has received regulatory approval for out-of-the-office use.

Table 1 lists the thresholds, which are commonly recommended in guidelines to differentiate normotension from hypertension on daytime, nighttime, and 24-hour ambulatory monitoring. The International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcome (IDACO) includes randomly recruited population samples who had office and ambulatory blood pressure and cardiovascular risk factors measured at baseline with follow-up of fatal and nonfatal cardiovascular outcomes.[32] In multivariable-adjusted analyses, we determined thresholds for the ambulatory blood pressure, resulting in 10-year cardiovascular risks similar to those associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), and high (140/90 mm Hg) blood pressure on in-office measurement.[33] These outcome-driven thresholds are shown in Table 2.

With regard to the time of day that is most predictive of outcome, several studies in patients[22–24] or populations[25,26] corroborated that nighttime compared with daytime blood pressure is a better predictor of cardiovascular complications. In the IDACO database,[27] nighttime blood pressure adjusted for daytime blood pressure, predicted total, cardiovascular, and noncardiovascular mortality. Conversely, adjusted for nighttime blood pressure, daytime blood pressure predicted only noncardiovascular mortality, with lower blood pressure levels being associated with increased risk.[27] Both daytime and nighttime blood pressure predicted all cardiovascular events and stroke.[27,28] Antihypertensive drug treatment removed the significant association between cardiovascular events and daytime blood pressure.[27] A subsequent IDACO publication clarified that isolated daytime hypertension and isolated nighttime hypertension both predicted adverse cardiovascular health outcomes.[34] In addition to the minimization of confounding by antihypertensive drug treatment, usually taken in the morning or during the day, the standardized conditions during sleep (supine position and absence of movement) probably explain why the nighttime blood pressure is the most accurate prognostic marker.[22–27] This is in keeping with the concept originally enunciated by Smirk in 1964 that elevation of basal blood pressure obtained following sedation was an accurate marker for adverse health outcomes.[35]

The major contribution of ambulatory blood pressure monitoring to risk stratification is the cross-classification between office and ambulatory blood pressure in both untreated people or treated patients. In clinical practice, the commonly used definition of white-coat hypertension is a raised in-office blood pressure in the presence of a normal daytime ambulatory blood pressure. Results of event-driven studies convincingly demonstrated that the risk of cardiovascular disease is lower in patients with white-coat hypertension than in those with raised ambulatory blood pressure, even after controlling for concomitant risk factors.[28] When daytime ambulatory blood pressure was below 130 mm Hg systolic and 80 mm Hg diastolic, the incidence of cardiovascular disorders did not differ between normotensive people and those with white-coat hypertension.[36] The counterpart of white-coat hypertension is masked hypertension, a disorder characterized by a normal in-office blood pressure confirmed at repeated clinic visits, but a raised daytime ambulatory blood pressure. Sustained hypertension refers to the joint elevation of both in-office and daytime blood pressure. In the IDACO database, using a threshold of 135/85 mm Hg, the prevalence of normotension and white-coat, masked, and sustained hypertension was 49.4%, 10.6%, 14.5%, and 25.5%, respectively. The multivariable-adjusted risk associated with white-coat hypertension did not differ from normotension, whereas masked hypertension conferred a risk approximating to that of sustained hypertension (Figure 1).[28]

In a further analysis of the IDACO database,[37] we explored whether in untreated participants ambulatory blood pressure monitoring refines risk stratification across classes of the office blood pressure according to the JNC7[38]/WHO-ISH[39] classification. We entered people with normal office and normal daytime ambulatory blood pressure as the reference group. Among participants with office normotension (<120/<80 mm Hg) or office prehypertension (120–139/80–89 mm Hg), respectively, 198 (7.5%) and 900 (29.3%) had

Table 2. Proposal for outcome-driven reference values for ambulatory blood pressure measurement

	24-Hour	Daytime	Nighttime
Optimal blood pressure (mm Hg)	<115/75	<120/80	<100/65
Normal blood pressure (mm Hg)	<125/75	<130/85	<110/70
Ambulatory hypertension (mm Hg)	≥130/80	≥140/85	≥120/70

Thresholds for the ambulatory blood pressure, resulting in 10-year cardiovascular risks similar to those associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), or high (140/90 mm Hg) blood pressure on office measurement. Reproduced with permission from the study of Kikuya *et al.*[33]

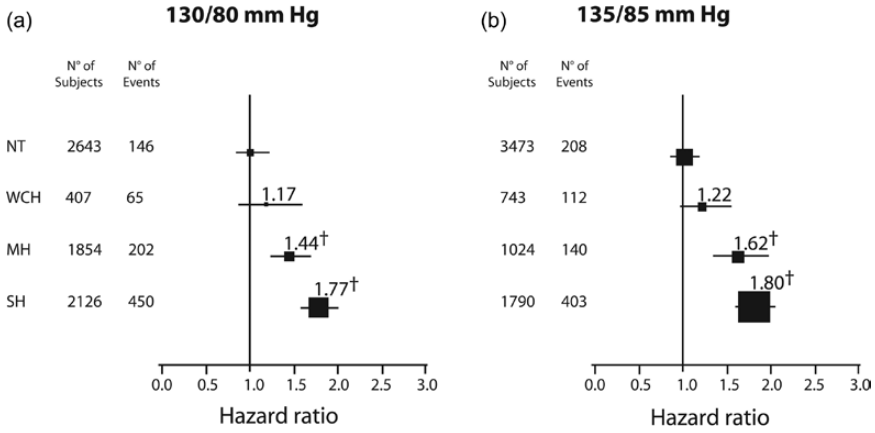

Figure 1. Hazard ratios for cardiovascular events according to the cross classification of conventional and daytime ambulatory blood pressure. NT, WCH, MH, and SH indicate normotension, white-coat hypertension, masked hypertension, and sustained hypertension, respectively. NT is the reference group (†$P < 0.001$). The analyses were based on lower [≥130/80 mm Hg (**a**)] and higher [≥135/85 mm Hg (**b**)] cut-off limits for daytime ambulatory hypertension and were adjusted for cohort, sex, age, body mass index, serum cholesterol, smoking and drinking, history of cardiovascular disease, diabetes mellitus, and antihypertensive drug treatment. Squares are proportional to the number of events per group. Horizontal lines denote the 95% confidence interval. (Reproduced with permission from the study of Hansen *et al.*[28])

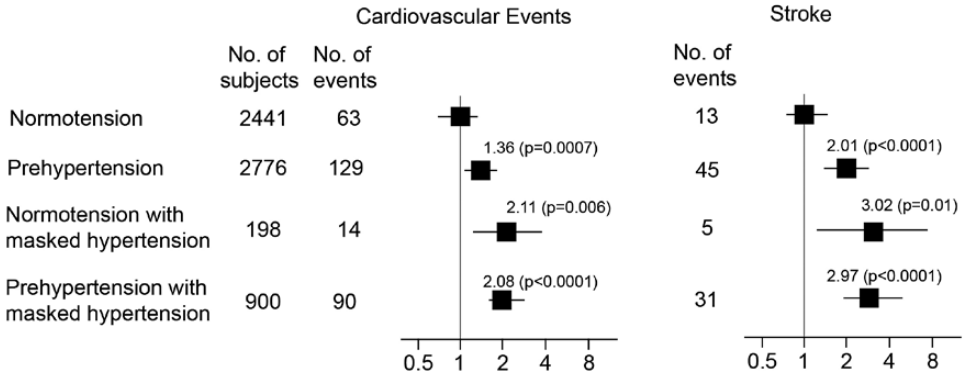

Figure 2. Hazard ratios for cardiovascular events and stroke associated with masked hypertension on daytime blood pressure monitoring in participants with normotension or prehypertension. Participants with true normotension are the reference group. Normotension (<120/80 mm Hg) and prehypertension (120–139/80–89 mm Hg) refer to the classification based on the conventional blood pressure according to the JNC7/WHO-ISH criteria. Thresholds for daytime hypertension were ≥135 mm Hg systolic or ≥85 mm Hg diastolic. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular complications, and diabetes mellitus. Horizontal lines denote the 95% confidence interval. Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.53 (95% confidence interval [CI], 1.23–1.91; $P = 0.0001$) for the composite cardiovascular endpoint and 1.48 (CI, 1.01–2.16; $P = 0.04$) for stroke. (Reproduced with permission from the study of Brguljan-Hitij *et al.*[37])

masked hypertension. Compared with true normotension, the multivariable-adjusted hazard ratios associated with masked hypertension in normotensive subjects, were 2.11 ($P = 0.007$) for a composite cardiovascular endpoint and 3.02 ($P = 0.01$) for stroke (Figure 2).[37] The corresponding hazard ratios associated with masked hypertension in prehypertensive subjects were 2.08 ($P < 0.0001$) and 2.97 ($P < 0.0001$), respectively. Compared to prehypertension without masked hypertension, the hazard ratios associated with masked hypertension in prehypertensive subjects were 1.53 ($P = 0.0001$) for the composite cardiovascular endpoint and 1.48 ($P = 0.04$) for stroke (Figure 2).[37] These findings remained consistent, if masked hypertension was defined based on the 24-hour or nighttime blood pressures.[37] Ambulatory blood pressure monitoring also enhances risk stratification in apparently normotensive people with optimal, normal, or high-normal office blood pressure, and who present with diabetes.[40]

The probability of having masked hypertension increases with an office blood pressure in the normal or high-normal range (odds ratio [OR], 5.1 vs. optimal office blood pressure), age 40 years or older (OR, 2.5 vs. being younger than 40 years), overweight or obesity (OR, 2.0), alcohol intake (OR, 1.9), diabetes mellitus (OR, 1.8), and smoking (OR, 1.5). Other risk factors include a family history of hypertension in both parents, patients with multiple risk factors for cardiovascular disease, male sex, and higher awake heart rate.[41]

Self-recording of blood pressure at home

Investigators from Leuven[42] and Dublin[43] promoted the use of home blood pressure monitoring in clinical research as far back as the 1970s: "Recordings of blood pressure over prolonged periods in ambulatory hypertensive patients

and normal subjects have shown striking variations…… They have served to emphasize that the casual blood pressure measurement, representing only 1/1400 of the total day's blood pressure, may be not only unrepresentative but frankly misleading, particularly in patients with borderline or labile hypertension."[43] The development of cheap and properly validated devices for blood pressure self-monitoring, over the past 20 years, carried this technique to clinical application.[9] Blood pressure self-measurement offers several of the well-recognized advantages of the more complex approach of ambulatory blood pressure monitoring.[42] The greater number of readings and the minimization of the white-coat effect contribute to a better diagnostic accuracy, compared with conventional sphygmomanometry.[42] If automated devices are used and if patients apply a standard protocol for the timing of the measurements rather than initiate recordings based on symptoms, self-recorded blood pressure values are to a large extent free of observer bias. Moreover, self-measurement of blood pressure increases adherence to antihypertensive drug treatment,[44,45] and allows reducing the number of clinic visits required for the diagnosis and treatment of hypertension,[46,47] and the assessment of long-term blood pressure variability.[48] However, it must be acknowledged that self-measurement of blood pressure is not as straight-forward as is often assumed. Firstly, devices used for self-measurement must be accurate. Rigorous scrutiny of the devices available on the market of self-measurement showed that of 1,536 listed on the internet, only 159 had any form of independent validation for accuracy. Of those, only 30 fulfilled current criteria for accuracy, which means that over 1,500 devices being used for self-measurement throughout the world might be inaccurate (http://www.medaval.org). Secondly, the procedure for self-measurement of blood pressure must be carefully executed. In order for a recorded blood pressure from self-measurement to approximate to the mean daytime blood pressure obtained with ambulatory monitoring, it is necessary to self-measure blood pressure twice in the morning and evening for 7 days and to calculate the average of 6 days measurement, having discarded the first day of measurement. This procedure is quite arduous and demanding on patients.[9]

Using the self-measured blood pressure at home, levels of 135 mm Hg systolic or 85 mm Hg diastolic or higher are considered hypertensive (Table 1). We derived outcome-driven thresholds for home blood pressure measurement in the International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO).[49] In multivariable-adjusted analyses of 6,740 people randomly recruited from 5 populations, we determined home blood pressure thresholds, which yielded 10-year cardiovascular risks similar to those associated with office blood pressure levels of 120/80 mm Hg, 130/85 mm Hg, 140/90 mmHg, and 160/100 mm Hg. The corresponding home blood pressure thresholds were 120/75 mm Hg, 125/80 mm Hg, 130/85 mm Hg, and 145/90 mm Hg, respectively.[49]

Over the past decade, studies in patients[50] and populations,[51,52] proved that the self-measured blood pressure is a better prognosticator of outcome than the in-office blood pressure. In the IDHOCO database,[53] using 135/85 mm Hg as a threshold for the home blood pressure, the number of participants with masked hypertension amounted to 42 (3.1%), 131 (12.9%), and 233 (22.5%) among participants with optimal, normal, and high-normal in-office blood pressure as defined in Table 1, respectively. Across these 3 categories of patients with masked hypertension (Figure 3), using optimal in-office blood pressure without masked hypertension as reference, the multivariable-adjusted hazard ratios for total mortality were 1.91 (95% confidence interval [CI], 0.98–3.74), 1.66 (CI, 1.04–2.63), and 1.47 (CI, 0.98–2.22). The corresponding hazard ratios for a composite cardiovascular endpoint were 2.14 (CI, 0.89–5.15), 1.96 (CI,

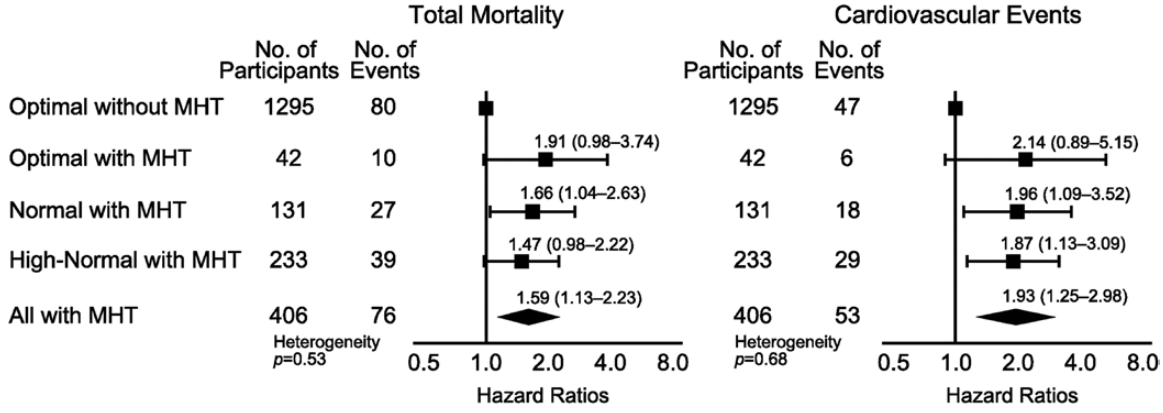

Figure 3. Hazard ratios associated with masked hypertension (≥135/85 mm Hg) on home blood pressure monitoring in participants with optimal, normal, or high-normal office blood pressure. Participants with optimal blood pressure without elevated home blood pressure was the reference group. Systolic/diastolic thresholds for the conventional blood pressure were optimal (<120/80 mm Hg), normal (120–129/80–84 mm Hg), and high-normal (130–139/85–89 mm Hg). When a systolic or diastolic blood pressure was in a different category, the participant was assigned to the higher category. Systolic/diastolic thresholds for hypertension on home measurement were ≥135/85 mm Hg. MHT indicates masked hypertension. The hazard ratios were adjusted for cohort, sex, age, body mass index, smoking, total cholesterol, diabetes mellitus, and history of cardiovascular disease. Horizontal lines denote the 95% confidence interval. MHT indicates masked hypertension. The diamond represents the pooled estimate in all patients with MHT. The *P* value for heterogeneity was derived by testing an ordinal variable in Cox proportional hazard regression coding for the 3 subgroups among patients with MHT. (Reproduced with permission from the study of Asayama *et al.*[53])

1.09–3.52), and 1.87 (CI, 1.13–3.09), respectively. We therefore confirmed that, in addition to the ambulatory blood pressure,[37] also the home blood pressure[53] refines risk stratification in apparently healthy people with normal or high-normal office blood pressure.

The question therefore remains whether self-monitoring of blood pressure at home can replace the gold standard in out-of-the-office blood pressure measurement, that is ambulatory blood pressure monitoring. The answer is definitely no. First, home blood pressure measurement does not allow easy recording of the blood pressure at night, the window of the day during which blood pressure is most predictive of adverse cardiovascular outcome.[22–28] Second, isolated nocturnal hypertension has a prevalence of 7% among Whites[34,54] and of 10% to 11% among Blacks[54] and Asians,[34,54,55] and confers a risk equal to that of an elevated daytime blood pressure.[54] Only 24-hour ambulatory blood pressure monitoring makes diagnosing isolated nocturnal hypertension straightforward. Third, ambulatory monitoring is the preferred instrument to diagnose hypotension, in particular in seniors, in whom postprandial and postural hypotension are common, because of impairment of the autonomic nervous system and the attenuated baroreceptor reflex. The diagnosis of symptomatic drug-induced hypotension is a key issue in patients who have a compromised arterial circulation, such as those with coronary and cerebrovascular disease and fragile elderly patients.[9] Fourth, whereas carotid atherosclerosis was associated with the home blood pressure in Japanese, the ambulatory blood pressure in the same cohort was a stronger predictor of silent cerebrovascular disease.[56] Finally and foremost, using home instead of ambulatory monitoring misses the high-risk diagnoses of masked or sustained hypertension in over 25% of patients.[57] Indeed, in 831 untreated outpatients (mean age, 50.6 years; 49.8% women), we measured office (3 visits), home (7 days), and 24-hour ambulatory blood pressures. We applied hypertension guidelines for the cross-classification of patients into normotension or white-coat, masked, or sustained hypertension (Table 1). Based on office and home blood pressures, the number (percentage) of patients with white-coat, masked, and sustained hypertension was 61 (10.3%), 166 (20.0%), and 162 (19.5%), respectively. Using daytime instead of home blood pressure confirmed the cross-classification in 575 patients (69.2%), downgraded risk from masked hypertension to normotension (n = 24) or from sustained to white-coat hypertension (n = 9) in 33 patients (4.0%), but upgraded the risk from normotension to masked hypertension (n = 179) or from white-coat to sustained hypertension (n = 44) in 223 (26.8%).[57] Analyses based on the 24-hour instead of the daytime ambulatory blood pressure were confirmatory. In adjusted analyses, both the urinary albumin-to-creatinine ratio (+20.6%; CI, 4.4–39.3) and aortic pulse wave velocity (+0.30 m/s; CI, 0.09–0.51) were higher in patients who moved up to a higher risk category.[57] Both indexes of target organ damage as well as the central augmentation index were positively associated ($P \leq 0.048$) with the odds of being reclassified to a higher risk category.[57]

BLOOD PRESSURE THRESHOLDS

The relation between cardiovascular complications and blood pressure is continuous at least down to a conventional blood pressure level of 115 mm Hg systolic or 75 mm Hg diastolic.[2] The continuous nature of the relation with blood pressure not only holds true in hypertensive patients, but in normotensive people as well, so that for instance of all strokes, three-fourths occur in individuals with normal blood pressure on conventional in-office measurement and only one-fourth in patients with office hypertension.[2] The epidemiological evidence does not reveal a sudden increase in the cardiovascular complications associated with blood pressure at the thresholds proposed in various guidelines and summarized in Tables 1 and 2. However, clinicians need numbers to diagnose hypertension and initiate or adjust antihypertensive drug treatment.

The wide variety of thresholds proposed in guidelines illustrate the debate as to whether the target blood pressure levels should differ according to sex or age or according to the presence of target organ damage, diabetes mellitus, or chronic kidney disease. Using IDHOCO data, we therefore did a subject-level meta-analysis of 5,018 people untreated for hypertension and randomly recruited from 5 populations (women, 56.7%; ≥60 years, 42.3%). We used multivariable-adjusted Cox regression and a bootstrap procedure to determine home blood pressure levels yielding 10-year cardiovascular risks similar to those associated with established systolic/diastolic thresholds (140–160/80–100 mm Hg) for the in-office blood pressure. Conversely, we estimated thresholds for the in-office blood pressure providing 10-year cardiovascular risks similar to those associated with established thresholds for the home blood pressure (125–135/80–85 mm Hg). Our analyses supported contemporary guidelines that propose single blood pressure thresholds that can be indiscriminately applied in both sexes and across the age range up to 80 years of age. In the very elderly, in the absence of strong evidence favoring treatment above observation, restraint should be the compass guiding clinicians in their decision to initiate or adjust antihypertensive drug treatment. Overtreatment is certainly an issue in the very elderly. In untreated octogenarians, a systolic home blood pressure of 152 mm Hg or more and a diastolic home blood pressure of less than 65 mm Hg entailed increased cardiovascular risk, whereas a diastolic home blood pressure above 82 mm Hg minimized risk.[58] In treated octogenarians, total mortality was curvilinearly associated with systolic home blood pressure. Levels below 127 mm Hg were associated with increased total mortality with 149 mm Hg being associated with lowest risk of death.[58]

AMBULATORY MONITORING AS TREATMENT GUIDE

The European Society of Hypertension position paper, although giving considerable attention to the diagnostic role of ambulatory blood pressure monitoring has relatively little to say on the use of this technique for initiating and following the efficacy of treatment[7]: "…The frequency of repeat ambulatory blood pressure monitoring to evaluate

the efficacy of antihypertensive medication will be dependent on the severity of hypertension and the response to treatment. In patients with severe hypertension and evidence of target organ damage, blood pressure reduction is urgent and in the initial stages of treatment, ambulatory monitoring may be required frequently as different drug combinations are introduced and dosage levels are altered. In patients with mild hypertension and no evidence of target organ involvement, ambulatory blood pressure monitoring has to be repeated less frequently according to the device availability, the individual patient's needs and preference, and the physician's discretion…." However, the potential benefit of the technique in influencing therapy was acknowledged[7]: "…An Irish study in primary care showed that only 12% of patients achieved target blood pressure with office blood pressure compared with more than one-third of patients with ambulatory blood pressure measurement. Furthermore, 38% of patients had a change in their medication as a result of ambulatory monitoring, 32% had a new medication started, and 14% of untreated patients with elevated office blood pressure, who were candidates for drug treatment, were not started on medication because their ambulatory blood pressure was normal…."

These brief statements constitute scarcely 1% of the entire position paper,[7] which hardly does justice to the potential benefit of ambulatory blood pressure monitoring in assessing treatment efficacy and the likelihood that this feature may well exceed the diagnostic benefits of the technique in clinical practice. This omission becomes particularly important in the context of the suboptimal blood pressure control rates, largely based on in-office blood pressure measurement, common to so many countries. The largest study to date on ambulatory blood pressure monitoring in primary care comes from Spain, where a nationwide project to promote the use this technique in primary care settings was established a decade ago.[59] One analysis of the Spanish database strongly supports the use of ambulatory monitoring as a means of gaining greater insight into the subtleties of drug effects on blood pressure.[59] The concluding messages from the Spanish study were that, compared to casual blood pressure measurement, ambulatory monitoring led to a reduction in the proportion of older subjects recommended for hypertension treatment and a substantial increase in the proportion of those whose hypertension was controlled.[59]

Initiation of treatment

The guidelines are unanimous in recommending ambulatory blood pressure monitoring in all patients under consideration for blood pressure lowering medication.[5–8] The rationale behind these recommendations is basically to confirm that the elevation of blood pressure is sustained on out-of-office measurement and not due to a white-coat reaction, as may occur in 25% of patients.[60]

Assessing initial treatment efficacy

However, we now must move into unchartered waters, because international guidelines have not, as yet, made definitive recommendations as to how ambulatory blood pressure monitoring should be used in assessing the efficacy of prescribed treatment. Of course, the same principles apply as for the use of ambulatory monitoring for the diagnosis of hypertension. Regardless of the patient's risk factor profile, there is a compelling need to achieve blood pressure reduction throughout the 24-hour period. Of course, if the risk factor profile of the patient is bad, for instance because of target organ damage, a history of cardiovascular disease or comorbidities, such as diabetes, the need to reduce blood pressure becomes more pressing. So having initiated treatment (and it is not within the scope of this review to discuss how this might be done), it would seem reasonable to repeat ambulatory monitoring within 3 to 6 weeks to determine if adequate blood pressure reduction has been achieved. If further adjustments in therapy are required, as may often be the case, then repeating ambulatory monitoring at 3-to 6- week intervals until control is achieved is justifiable. There is, however, another aspect of treatment that merits consideration, namely, excessive lowering of blood pressure, especially of the nocturnal pressure. Excessive elevation of nocturnal blood pressure entails cardiovascular risk, but a group of patients may be adversely affected by excessive lowering of the nocturnal blood pressure.[61] Up titration of treatment based on the office blood pressure cannot reveal nocturnal hypotension.

Assessing long-term efficacy

Once control of daytime and nighttime ambulatory blood pressure has been achieved, ambulatory monitoring need only be repeated at 6-monthly or annual intervals. Self-measurement of blood pressure at home can be used to obtain confirmatory evidence that blood pressure control is being maintained, at least for the daytime blood pressure.[62] However, to obtain a self-measured blood pressure equivalent to the daytime ambulatory blood pressure, 6 days of measurement are required, 2 readings in the morning, and 2 in the evening, after discarding the measurements from the first day. Many patients and doctors consider this as being more onerous than performing ambulatory monitoring, which in addition provides the nocturnal blood pressure, the best predictor of outcome.[22–27,55]

CLINICAL IMPLEMENTATION

The rational management of hypertension inevitably starts with accurate measurement of blood pressure. The data currently reviewed suggest that ambulatory monitoring might be indicated in normotensive and prehypertensive people to screen for masked hypertension, a condition that confers a risk approaching that of sustained hypertension. However, robust evidence for the routine implementation of ambulatory blood pressure monitoring as a screening tool for masked hypertension should come from randomized clinical trials that prove that the early diagnosis and treatment of masked hypertension reduce the incidence of cardiovascular complications. Such trials are needed in view of the persistence of masked hypertension.[63] In the meantime, a diagnostic work-up of patients, making

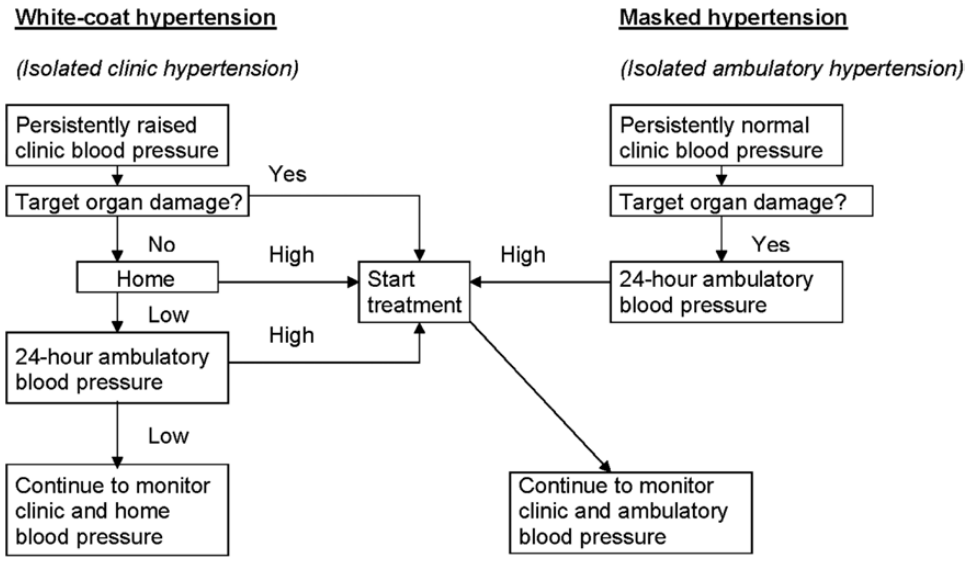

Figure 4. Diagram for evaluation of patients by use of office, home, and ambulatory monitoring of blood pressure. (Reproduced with permission from the study of Staessen *et al.*[64])

use of office, home, and ambulatory blood pressure, as summarized in Figure 4,[64] might help clinicians, while not putting too large a burden on the health care system. With recent advances in all measurement technologies, it is time for manufacturers to produce accurate, inexpensive, user friendly and versatile "devices for all seasons" that will allow doctors, pharmacists, and patients to measure office, home, and ambulatory blood pressure, according to the indication with the means for appropriate transmission, storage, and analysis of the data.

To be equitable, health insurance should provide easy access to the diagnostic procedures that allow risk stratification on the basis of blood pressure and the rational use of antihypertensive drugs. Failure to provide adequate reimbursement for ambulatory blood pressure monitoring is in conflict with what authoritative bodies[5–8] have unequivocally recommended. From a European perspective, ambulatory blood pressure monitoring is not reimbursed in Belgium, Denmark, France, and Spain. The National Health Service in the United Kingdom provides free access to health care, including ambulatory blood pressure monitoring. In Ireland (€60 per recording in general practice), Norway (€40 per recording in primary and specialized care), and Finland (free of cost or €60 per recording in public and private health care, respectively) ambulatory blood pressure monitoring is covered by health insurance. In Ireland, pharmacies contribute to making ambulatory blood pressure monitoring more accessible at a cost for patients varying from €40 to €100 per recording. Self-measurement of blood pressure is not reimbursed in any of the aforementioned countries with the exception of Denmark. In this country, home blood pressure measurement is reimbursed on condition that hypertension is likely to be present based on office blood pressure readings at 2 or more visits and in case of resistant hypertension or large variability in the office blood pressure readings. In China, ambulatory blood pressure monitoring is covered by health insurance at a cost varying from €12 to € 45 per recording in both primary and referral hospitals, but home blood pressure monitoring is not reimbursed. One of us (Y.L.) in collaboration with an internet company (Shuoyun Information Technology Company Ltd, Shanghai, China) developed a web-based ambulatory blood pressure reporting system (www.shuoyun.com.cn). This web-based system allows experts at tertiary hospitals to assist locally practicing primary care physicians with the interpretation of ambulatory blood pressure recordings.

Several studies addressed the cost-effectiveness of ambulatory blood pressure monitoring. Originally, the idea was put forward that out-of-the-office treatment would reduce health care costs mainly by avoiding antihypertensive drug treatment in white-coat hypertensive patients.[65–67] In 2004, Krakoff computed the cost savings likely to take place when ambulatory blood pressure monitoring would be implemented in newly detected hypertensive patients.[68] His calculations accounted for the contemporary costs of testing and treatment, the prevalence of white-coat hypertension at baseline, while varying the incidence of new-onset hypertension after the initial screening. The results indicated potential savings of 3% to 14% for the cost of care for hypertension and a 10% to 23% reduction in treatment days when ambulatory blood pressure monitoring would be incorporated into the diagnostic process.[68] The cost of ambulatory blood pressure monitoring for secondary screening on an annual basis would be 10% of treatment costs. Krakoff estimated that savings for use of ambulatory blood pressure monitoring could be generated, if the annual treatment costs were as little as $300.[68] In 2011, Lovibond *et al.* published a Markov model-based probabilistic cost-effectiveness analysis.[69] These investigators used a hypothetical primary-care population aged 40 years or older with screening blood pressure measurements greater than 140 mm Hg systolic and 90 mm Hg diastolic and a risk factor prevalence representative for the general population. Lovibond *et al.* compared 3 diagnostic strategies—further blood pressure measurement in the clinic, at home, and with

an ambulatory monitor in terms of lifetime costs, quality-of-life-adjusted life years, and cost-effectiveness. Ambulatory monitoring was the most cost-effective strategy for the diagnosis of hypertension for women and men of all ages. It was cost-saving for all groups (from –£56 (CI, −105 to −10) in men aged 75 years to –£323 (CI, −389 to −222) in women aged 40 years) and resulted in more quality-of-life-adjusted life years for women and for men older than 50 years. These findings were robust when assessed with a wide range of deterministic sensitivity analyses around the base case, but was sensitive if home monitoring was judged to have equal test performance to ambulatory monitoring.[69] However, as outlined in our review, home blood pressure measurement cannot completely cover what ambulatory monitoring provides in terms of clinical information. To our knowledge, none of the published cost-benefit estimates accounted for the 15% prevalence of masked hypertension in the general population and the associated adverse health outcomes that equal those of sustained hypertension.

CONCLUSIONS

The take-home message of this review is that ambulatory blood pressure monitoring is the state-of-the-art technique of blood pressure measurement and is indispensable for the diagnosis of hypertension and for the decision to initiate or adjust antihypertensive drug treatment. In an era, in which the cost for the equipment required for ambulatory monitoring is decreasing, health care providers should facilitate a generalized access to this state-of-the-art technology without limitations in terms of the frequency of the recordings. Manufacturers might support this effort by designing versatile devices that can be used for all types of blood pressure measurement and by considering market size rather than profit margins per single device sold. The only provision on which one should never compromise is that physicians and nurses, be it in primary or specialized care, have to prove that they have acquired the skills necessary for understanding the principles of blood pressure measurement, cuff fitting, monitor function and analysis, and interpretation of ambulatory blood pressure recordings. One sentence summarizes it all: "Raising the pressure on hypertension,[55] the leading cause of cardiovascular death worldwide, requires accurate blood pressure measurement for its diagnosis and management." This cannot be done without ambulatory blood pressure monitoring.

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DISCLOSURE

The authors have no conflict of interest.

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