Abstract: This article reviews the clinical value of ambulatory blood pressure (BP) vis-à-vis the traditional BP measurements taken in the physician’s office or in the hospital. Mention is initially made that longitudinal studies conducted in the general population or in hypertensive cohorts have shown that ambulatory BP provides a more accurate prediction of outcome than office BP. Namely, that (1) the risk of cardiovascular events increases in a less steep fashion with office than with 24-hour mean BP, (2) the 24-hour BP-dependent prediction is maintained after adjustment for office BP values, and (3) among individuals with normal office BP, those with increased ambulatory BP (masked hypertension) have an increased prevalence of organ damage, a more frequent unfavorable metabolic profile and a higher risk of new onset sustained hypertension, diabetes mellitus, and cardiovascular events than those with normal ambulatory BP. It is further mentioned, however, that more recently similar observations have been made for individuals with high office but normal ambulatory BP (white coat hypertension) suggesting a complementary role of out-of-office and office BP values in the determination of patients’ prognosis. The evidence in favor of an independent prognostic value also of some within 24-hour BP phenomena (night BP reduction or absolute values, short-term BP variations, and morning BP surge) is then critically appraised for its elements of strength and weakness. Finally, whether the clinical advantages of ambulatory BP make this approach necessary for all patients with hypertension is discussed. The conclusion is that this is at present still premature because crucial evidence pro or against routine use of this approach in untreated and treated hypertensives is not yet available. It will be crucial for future studies to determine whether, compared with a treatment guided by office BP, a treatment tailored on ambulatory BP allows to improve prevention or regression of organ damage as well as protection from major cardiovascular complications to a degree that justifies the complexity and cost of the procedure. (Circ Res. 2015;116:1034-1045. DOI: 10.1161/CIRCRESAHA.116.303755.)

Key Words: blood pressure ■ cardiovascular diseases ■ end-stage renal disease ■ hypertension ■ masked hypertension ■ white coat hypertension
Several considerations justify the great interest on ambulatory blood pressure (BP) for the diagnosis and treatment of hypertension that has occurred all over the world in the past few decades. One, it is well known that during the 24 hours BP is by no means stable but it undergoes marked variations.1,2 Two, because of these variations office BP shows a limited relationship with the average 24-hour day or night-time BP values, the correlation coefficients rarely exceeding 0.3 or 0.4 in hypertensive patient cohorts.3 Three, 24-hour BP values are lower than office BP, and progressively more so as age increases or office BP becomes progressively more elevated.4 Four, limited correlations and marked differences between the 2 pressures extend to the treated state because the office BP reductions induced by treatment show not only marked quantitative but also qualitative differences from those taking place during the 24 hours. Namely, a treatment-induced pronounced office BP reduction may be accompanied in the same patient by a small reduction, no reduction or even an increase of 24-hour BP, and vice versa.3 Finally, although the amount of epidemiological data remains largely in favor of office BP,5 evidence is available that ambulatory BP may more accurately grade the severity of hypertension and predict the cardiovascular risk of the patient, presumably because it more accurately reflects the load of BP on the heart and the vessels. Furthermore, ambulatory BP may help to more accurately determine the progression of atherosclerosis (the vascular lesion that accounts for the largest portion of hypertension-related complications), as suggested by the observation that an important component of atherosclerosis initiation and progression such as endothelial dysfunction is more clearly impaired in patients with abnormal than in those with a preserved circadian BP profile.6,7 All these have important implications for the treatment strategies to be adopted as well as for the appreciation of the protective effect of the prescribed therapy, which explains why some investigators and clinicians think that this approach should be routinely used in the management of hypertension, a position reflected in some recent guidelines.8

This article will review the evidence on the prognostic value of ambulatory BP. It will further show that patient prognosis may be additionally modulated by BP phenomena occurring within the 24 hours. It will also mention, however, that important gaps of knowledge exist, that research tools have sometimes inherent limitations and that further studies are needed before ambulatory BP enter routine use.

**Average 24-Hour, Daytime, and Night-Time BP**

After the landmark report by Perloff et al,9 the prognostic value of ambulatory BP has been investigated in several cross-sectional and longitudinal studies on general populations and hypertensive patients, in which ambulatory BP has been analyzed either as a continuous variable or by means of arbitrary working categories. The former approach has the advantage of removing the potential bias associated with the arbitrary definition of BP normality, whereas the latter offers a more clear decisional support to clinicians whose daily practice is largely founded on use of cutoff values. At any rate, either approach has almost invariably shown that (1) subclinical organ damage is more closely correlated with 24-hour mean than with office BP10 and (2) 24-hour mean systolic or diastolic BP has a steeper relationship with cardiovascular morbid or fatal events than the corresponding office BP values (Figure 1).11–17 This can to some extent be...
explained by the fact that, compared with office BP, 24-hour mean BP has a narrower distribution in the general or hypertensive populations. However, evidence has been obtained that 24-hour average systolic or diastolic BP predicts cardiovascular events also when data are adjusted for office BP (Figure 2) which provides support to its superior prognostic value. This has lately been confirmed by the analysis of a large database from several populations with a worldwide distribution who were followed up for \( \approx \)10 years. In the same database confirmation has also been obtained that, as suggested by previous population studies, an office BP value of 140/90 mm Hg approximately corresponds to a 24-hour average BP of 130/80 mm Hg. This has been the upper normality 24-hour mean value adopted by the European Society of Hypertension, the corresponding upper normality values for day and night times being defined as 135/85 and 120/70 mm Hg, respectively.

**Day/Night BP Cycle**

Early recordings of intra-arterial BP in ambulant subjects have shown that BP is characterized by a circadian pattern, with values that peak during the day and fall, normally to a substantial degree, at night. This has been later shown also by means of noninvasive ambulatory BP monitoring, which has emerged as a valid approach to an appropriate quantification of the sleep-wake BP cycle by the demonstration that the intra-arterially measured nocturnal hypotension is not disturbed by the potential inconveniences (noise, device weight, cuff inflations, etc) associated with the noninvasive monitoring procedure. It has thus become feasible to address the prognostic value of the nocturnal BP reduction and night-time values in large-scale cross-sectional or longitudinal studies (an approach precluded to intra-arterial BP monitoring) with the following main results.

**Dippers and Nondippers**

O’Brien et al and Pickering originally proposed to classify subjects as nondippers or dippers according to the magnitude of their nocturnal hypotension. This has gained wide acceptance and it has now become customary to regard as nondippers and dippers individuals with a fall of mean night-time BP \(<10\%\) and \(\geq 10\%\) than the average daytime values, respectively. Dippers may also be defined by a night/d BP ratio \(\leq 0.9\). Evidence that the nondipping phenomenon is prognostically adverse has grown in a consistent fashion and is now multifold and robust. Cross-sectional studies have shown that both left ventricular hypertrophy and ventricular arrhythmias are more common and severe in patients with blunted than in those with a normal day–night BP difference. Furthermore, a blunted day–night BP fall has been associated with a reduced brain matter volume, a steeper decline of cognitive functions, and a more evident silent cerebrovascular disease. Finally, a positive link has been consistently reported between a reduced BP dipping and markers of renal dysfunction such as albuminuria, impaired sodium excretion, and reduced glomerular filtration rate. This provides strong support to the conclusion that vital organ damage can be more advanced when BP load is persistently elevated throughout the 24 hours than when it is limited to the daytime only, with a load reduction during the several night hours that are spent asleep. Evidence is also available on the association between day–night BP changes and cardiovascular or renal outcomes in longitudinal studies with extended observational periods. In hypertensive individuals, O’Brien et al reported years ago a more frequent history of stroke in nondippers than in dippers. Staessen et al later showed that in patients with isolated systolic hypertension cardiovascular risk was greater if, after controlling for the 24-hour average BP level, nocturnal hypotension was less pronounced, the risk of cardiovascular events showing a significant 41% increase when the day–night systolic BP ratio (the inverse of the day–night BP fall) increased by 10%. Verdecchia et al observed that in the initially untreated hypertensive patients of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) nondippers at a baseline evaluation had, during the follow-up, a much greater risk of major cardiovascular events than dippers. The difference remained significant after controlling for age, sex, smoking, diabetes mellitus, and other potential confounders, and the results were confirmed in a subsequent larger sample in which the day–night BP ratio was analyzed as a continuous variable.

The prognostic importance of the day–night BP reduction has also been documented in population-based longitudinal studies, that is, studies that predominantly include individuals with a normal BP. In the Ohasama Japanese population, nondippers showed an \(\approx 2.5\) significant increase in cardiovascular mortality compared with dippers. Likewise, in the North Italian population addressed by the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, patients in whom nocturnal BP fall was less than the median value showed, during an \(\approx 12\) year follow-up, a similarly marked increase of cardiovascular mortality compared with subjects in whom the fall was greater than the median value. There thus seems to be no question that, regardless the ethnicity, the extent to which BP falls at night has an important prognostic relevance, and that this is the case not only when BP is elevated but also, as in the general population, when it is predominantly normal.

**Reverse and Extreme Dippers**

The original classification of patients into dippers and nondippers has been subsequently extended to include the so-called...
(1) reverse dippers or night BP risers, that is, individuals in whom there is no BP reduction during the nighttime or even a nocturnal hypertension and (2) extreme dippers, that is, individuals in whom the nighttime BP fall is regarded as excessive (ie, >20% of the daytime values). Although the prognostic value of the extreme dipping phenomenon remains controversial, evidence is available that the increase of cardiovascular risk may be particularly marked in patients in whom BP does not fall or increases at night. In the initially untreated hypertensive cohort studied by Verdecchia et al, the risk of cardiovascular events was much more pronounced when nighttime BP increased than when it was reduced, albeit within the nondipper range. This was the case also in the Ohasama population in which, compared with dippers, the risk of cardiovascular events was progressively greater as night-time BP increased than when it was reduced, albeit within the nondipper range. This was the case also in the Ohasama population in which, compared with dippers, the risk of cardiovascular events was much more pronounced when nighttime BP increased than when it was reduced, albeit within the nondipper range. It is reasonable to speculate that the high cardiovascular risk associated with these 2 highly prevalent conditions is at least in part caused by loss of the circadian control of BP, which is important in the pathogenesis of cardiovascular disease.

Night-Time BP Values

Additional support to the prognostic importance of the day–night BP cycle comes from the evidence that absolute nighttime BP values are prognostically superior to the daytime ones. In the PAMELA study, a 10 mm Hg increase of nighttime systolic BP was accompanied by a much greater increase of cardiovascular mortality than a 10 mm Hg increase of daytime systolic BP regardless of the baseline BP level at which the increase occurred (Figure 4). In the Dublin outcome study (follow-up 8.4 years), the same increase in night and day systolic BP led to an increase of cardiovascular mortality of 21% and 12%, respectively. In a meta-analysis of the available contributions to the issue of the prognostic value of the extreme dipping phenomenon remains controversial, evidence is available that the increase of cardiovascular risk may be particularly marked in patients in whom BP does not fall or increases at night. In the initially untreated hypertensive cohort studied by Verdecchia et al, the risk of cardiovascular events was much more pronounced when nighttime BP increased than when it was reduced, albeit within the nondipper range. This was the case also in the Ohasama population in which, compared with dippers, the risk of cardiovascular events was much more pronounced when nighttime BP increased than when it was reduced, albeit within the nondipper range. It is reasonable to speculate that the high cardiovascular risk associated with these 2 highly prevalent conditions is at least in part caused by loss of the nocturnal BP fall.

Further Considerations and Data Limitations

The reason for the prognostic superiority of night versus daytime BP is unclear, although it is widely thought that, compared with the daytime, night-time BP values are less affected by the variable interference of individual diurnal activities, thereby more accurately reflecting the usual or true daily life BP status of the patient. Knowledge is limited and data are insufficient on several other counts, however. One, whether the protective effect of nocturnal hypotension resides in the magnitude of the BP fall or in the absolute low night-time BP value is unclear, although recent observations that in subjects with nocturnal hypertension (mean night-time BP ≥120/70 mm Hg) the prevalence of organ damage does not majorly differ between dippers and nondippers suggests that the latter may be the case. Two, although the prognostic value of ambulatory systolic BP has usually been found to be greater than that of ambulatory diastolic BP, little information has been collected on the role, if any, of ambulatory pulse pressure, and in particular whether any predictive value should be ascribed to the pulse pressure reduction that systematically takes place from the day to the nighttime. Three, it also remains unclear whether different definitions of the day and night affect the prognostic

Figure 3. Cumulative incidence of cardiovascular events in dippers, nondippers, reverse dippers, and extreme dippers. For definition see text. Figure created with data derived from Verdecchia et al.

Figure 4. Increase in the risk of cardiovascular (CV) death for a 10 mm Hg increase in systolic blood pressure (SBP) at different initial SBP values. Data from the Pressioni arteriose monitorate e loro associazioni (PAMELA) population with a follow-up of 148 months. Figure created with data derived from Sega et al.
impact of their BP values. In ≈3000 initially untreated hypertensive patients who generated 356 cardiovascular events and 176 deaths during a 7-year follow-up the area under a receiver operating characteristic curve did not differ between different definitions of the day and night BP. Namely, the predictive ability for the in-study outcomes was similar when the day and night durations were defined by wide fixed-clock intervals (6:00 am to 10:00 pm for the day and 10:00 pm to 6:00 am for the night), narrow fixed-dose intervals (10:00 am to 8:00 pm for the day and midnight to 6:00 am for the night) or according to patient’s diary. However, including in a calculation the transitional times, that is, the hours during which some patients may be asleep, whereas others are awake, represents a source of data inaccuracy. Finally, there is also no question that the degree of nocturnal hypotension may be markedly affected by the quality and quantity of sleep, a factor which can vary between patients and also within a given patient from one recording to another. This is primarily responsible for the observation that in patients with a stable antihypertensive treatment and BP, ≈40% of dippers or nondippers at a first ambulatory BP monitoring changed status at a monitoring performed few months later. It further explains why in a large number of treated hypertensive patients nighttime BP showed a progressive increase as the perceived duration of sleep decreased from usual to <2, 2 to 4, and >4 hours below usual, the change showing no effect on daytime BP (Figure 6). Most importantly, in these patients, the incidence of total cardiovascular events and death was greater only in the group of nondippers in whom the perceived sleep duration was usual or only <2 hours from usual. These data clearly indicate that the prognostic value of the nondipping status requires evidence that failure of BP to show an appropriate night-time reduction was not caused by a poor sleep night. They also indicate that a more stringent definition of the dipping status may be advisable, such as, for example, that based on 2 separate 24-hour BP monitorings or by a single monitoring prolonged for 48 hours. Evidence has been obtained that in subjects defined as nondippers by 2 rather than 1 night-time the prognostic difference between dippers and nondippers is more evident. A more stringent definition should be used also in studies aiming at determining whether a nondipping status can be reversible by treatment. At present, limited evidence exists that this may be the case with diuretics or dietary restrictions of sodium intake, possibly because sodium absorption from the extra to the intravascular compartment opposes the night-time BP fall.

**Morning BP Rise**

Several cardiovascular events, including myocardial infarction, stroke, and sudden death peak in the first part of the morning. This has a pathophysiological explanation because transition from sleep to the wakefulness state is associated
with several bodily modifications that have a potential adverse effect on the cardiovascular system, that is, a marked and steep increase of BP and heart rate,\(^2\) a sympathetic activation and thus an increase of plasma catecholamines,\(^60,69\) an increase of platelet adhesiveness,\(^20\) and a reduction of fibrinolytic activity.\(^71\) Participation of the increased BP to the peak morning cardiovascular events has been reported by 2 studies performed in Japan, which have shown a direct association between the arousal-dependent pressor effect and the risk of total\(^72\) and haemorrhagic\(^73\) stroke. Further support has come from the International Database of Ambulatory blood glucose in relation to Cardiovascular Outcome, which has shown, based on a number of events much larger than that available in the Japanese studies, that a greater morning BP rise was accompanied by a greater risk of cardiovascular and all-cause mortality, although the association did not specifically extend to stroke.\(^74\) The issue is far from being conclusively documented, however, because these results were not confirmed in a large population of initially untreated hypertensive patients in whom a blunted morning BP surge was accompanied by an increase in the risk of cardiovascular events, rather than by the expected decrease.\(^44\) Furthermore, the magnitude of the morning BP rise has recently been found to have no relationship with the risk of cardiovascular events in the population of the PAMELA study during a follow-up of 16 years.\(^75\) A current working hypothesis is that, because of ethnic differences, the morning BP rise phenomenon may be more pronounced and clinically significant in Asian than in Caucasian individuals.

**Additional Considerations and Limitations**

Studies on the clinical relevance of the morning BP surge face formidable difficulties. First, because noninvasive ambulatory BP monitoring only provides few values per night-time hour (usually 2 or 3) the true BP levels in the period immediately preceding arousal may escape recognition. Second, because the morning BP surge has an inverse relationship with the night-time BP levels (ie, it is, as expected, progressively greater as night-time BP is progressively lower), its adverse prognostic role may be partly or entirely masked by a factor that exerts in parallel a protective effect. This can explain the paradoxical increase of cardiovascular risk that was observed with a reduced magnitude of the morning BP surge in the previously mentioned data from a hypertensive cohort.\(^44\)

Finally, no chance exists that the few BP values provided by noninvasive ambulatory BP monitoring can measure, in addition to the morning-sleep BP difference, the slope of the BP increase that occurs at arousal, a dynamic phenomenon that is completed within \(\approx 1\) to 2 minutes.\(^76\) It has thus been impossible, to date, to determine whether a steeper arousal-related BP increase has adverse cardiovascular consequences via, for example, the disruption of an unstable plaque or the sudden increase of cardiac afterload in the presence of a reduced coronary reserve. This will only be addressable by precise electroencephalographic identification of the awakening time coupled with beat-to-beat BP monitoring, an approach, however, hardly compatible with the sample size necessary to calculate cardiovascular risk.

**BP Variability**

It has long been known that, in addition to day-night BP changes, 24-hour BP is characterized by short-term variations that are particularly marked and frequent during the day but that also occur, albeit to a lesser degree, during the night-time.\(^77\) Evidence has been obtained that these variations largely depend on people’s behavioral activities but that nonbehavioral factors favoring or opposing BP changes are also involved, their influence on the heart and peripheral circulation being predominantly mediated by the autonomic nervous system and vasoactive substances with local or more widespread effects.\(^78\) It has further been established that BP variability increases with age and that it bears a close direct relationship with the mean BP level.\(^2,77,78\) Within subjects the magnitude of BP variations becomes greater as the mean BP during the period where these variations are calculated.\(^79\) Between subjects, 24-hour BP variability shows a progressive increase from normotension to mild and more severe hypertensive states either when BP is categorized by office or when it is categorized by ambulatory BP values.\(^2\)

**Prognostic Value**

Years ago, a state of increased variability, defined as labile hypertension, was thought to precede and favor progression to an established or sustained hypertensive state. Although this has never received firm experimental support from animal and human studies,\(^79\) evidence has in the meantime grown that the short-term BP variations that occur during the 24 hours have a damaging effect on the heart, the large arteries, and the small vessels that make 24-hour BP variability a cardiovascular risk factor independent of, and additional to, the risk brought about by 24-hour average BP. Cross-sectional studies have shown that, for any given level of 24-hour mean BP, echocardiographic left ventricular hypertrophy, carotid intima-media thickness, and organ damage in general are more pronounced or common when the SD of 24-hour mean BP values (a comprehensive measure of 24-hour BP variability) is greater.\(^78,80,81\) Furthermore, longitudinal studies have documented that an increase of 24-hour or daytime BP variations is associated with an increased development of cardiac and vascular damage as well as with a greater incidence of cardiovascular morbidity and mortality, this being the case also when data are controlled for the role concomitantly played by mean BP levels.\(^52-57\) To quote few examples, Sander et al\(^83\) showed that hypertensive patients with a greater 24-hour BP SD exhibited, during a few year follow-up, not only a greater carotid wall thickening but also an increased risk of cardiovascular morbidity and fatal events. Verdecchia et al\(^87\) showed that during a long follow-up initially untreated hypertensive patients exhibited an increased risk of cardiac events if BP variability was greater, although the predictive value was limited to the variability occurring during the night-time. Kikuya et al\(^80\) observed that in a Japanese population, subjects with a daytime SD of systolic BP \(<15.8\ \text{mmHg}\) had a lower incidence of cardiovascular mortality than subjects with a SD above this cutoff value. Finally, Mancia et al\(^42\) found, also in a general population, that the short-term erratic or residual BP changes that contribute to overall 24-hour BP variability in addition to its cyclic components (day–night and postprandial
variations) have a significant long-term relationship with cardiovascular and all-cause mortality (Figure 7). The relationship was independent of other cardiovascular risk factors and the adverse impact of BP variability was more important than that attributable to the 24-hour mean BP or, in a protective direction, the day–night BP difference, a +1 SD of the mean erratic variability value being accompanied by a 24% increase of cardiovascular risk.

Limitations
Studies on BP variability have important limitations. Its mechanistic aspects are still incompletely clear and no conclusive evidence exists on whether the magnitude of the 24-hour short-term BP variations can be reduced by antihypertensive treatment over and above the reduction passively accompanying a treatment-induced fall in 24-hour mean BP. It is also unknown whether the cardiovascular events associated with 24-hour BP variability can be reduced by treatment or they rather represent a nonmodifiable portion of the overall cardiovascular risk, perhaps contributing to the high residual risk that characterizes patients with an adequate BP control.

Finally, and most importantly, studying 24-hour short-term BP variations by noninvasive ambulatory BP monitoring faces an insurmountable problem that intermittent BP readings provide only a microscopic fraction (n <100) of the hundred thousand values that compose the 24-hour BP profile. If readings are spaced by >15 minutes, the resulting 24-hour SD can be unreliable but even shorter between-reading intervals cannot prevent a substantial loss of the overall variability phenomenon as well as of its various shorter and longer components.

The most crucial progress for BP variability studies will thus be to develop devices that measure beat-to-beat ambulatory BP noninvasively, thereby allowing not only a precise quantification of the overall magnitude of the BP variations but also an in-depth analysis of its various components and patterns. When (and if) available, beat-to-beat noninvasive BP monitoring will (or would) also allow to measure the slope of the steep increase of BP over the transition from sleep to morning arousal as well as to determine more in general the clinical significance of the speed of daily life BP changes. Beat-to-beat BP studies have shown the spontaneous BP increases and reductions that occur during the 24 hours to develop faster in hypertensive than in normotensive subjects, but no information is available on whether this has clinical relevance.

White Coat and Masked Hypertension
The use of ambulatory (and home) BP measurements has allowed to disclose 2 conditions that were unknown when measurements were limited to the clinic environment, that is, masked hypertension and white coat hypertension (WCH).

In masked hypertension, out-of-office BP is high and BP values in the physician’s office are normal, whereas in WCH the reverse is the case, that is, out-of-office BP is normal, whereas office BP is persistently elevated. The original definition of WCH is based on the belief that this condition is caused by the alerting reaction and transient BP rise that accompany the physician’s visit but because other factors may also be involved, a more descriptive terminology, that is, isolated office hypertension is also frequently used. For both masked hypertension and WCH the definition applies to untreated patients because in treated patients (1) the office-ambulatory BP discrepancy may be caused by a different drop of one versus the other pressure (because of the time of administration, the duration of the effect, and other reasons) and (2) patients may thus have had originally a sustained rather than a WC or masked hypertension condition. Both conditions offer a chance to verify the prognostic relevance of office versus ambulatory BP in the clinical setting, which makes them relevant for the present review.

Masked Hypertension
Although properly conducted studies are rare, the prevalence of masked hypertension is thought to be 10% to 15% of the general population which means that physicians should expect no less than 1 of 6 or 7 subjects with a normal office BP to have elevated ambulatory (or home) BP values. When this is found, further examinations are mandatory because data are remarkably consistent that in masked hypertension (1) there is a greater prevalence and severity of metabolic risk factors, including overweight, dyslipidemia, impaired glucose tolerance, and diabetes mellitus; (2) subclinical cardiac, vascular, or renal damage is more common; (3) the long-term risk of developing sustained hypertension, diabetes mellitus, or left ventricular hypertrophy is 2 to 3 times greater than that of individuals with normal in- and out-of-office BP; and (4) there

Figure 7. Adjusted hazard ratio (HR) of cardiovascular (CV) or all-cause death for 1 SD increase of different measures of diastolic blood pressure (BP) variability in the population of the Pressioni arteriose monitorate e loro associazioni (PAMELA) study. BP variability measures were: 24-hour day and night SD of the respective mean values; day–night BP ∆; and residual or erratic component of 24-hour BP variations after removal of the main cyclic components by Fourier analysis of the BP tracing. Follow-up was 148 months. Data were adjusted for age, sex, previous CV events, smoking, serum cholesterol, plasma glucose, and 24-hour average blood pressure. Figure created with data derived from Mancia et al.
is also a greater incidence of cardiovascular morbid and fatal events, with an overall risk that is either intermediate or, in some studies, closer to that of sustained hypertension than to true normotension. This represents a sort of a proof of concept of the prognostic impact of ambulatory, and more in general out-of-office BP values vis-à-vis the traditional BP classification based on office BP measurements only.

**White Coat Hypertension**

In an early study conducted in untreated hypertensive patients, cardiovascular morbidity was found to be lower in WCH than in ambulatory hypertension, and not dissimilar between WCH and clinical normotension. Similar data were later reported in a mixed population of treated and untreated individuals. Furthermore, the prevalence of organ damage and the incidence of cardiovascular events were found to be comparable in WCH and true normotension in other studies, strengthening the belief that daily life BP was the prognostically relevant pressure. It should be emphasized that an important requirement for a correct interpretation of the prognostic significance of WCH is for this condition to be defined by low (restrictive) values of ambulatory BP to limit inclusion of people with a somewhat elevated daily life BP (and hence a potentially high risk) under the definition of WCH. This was done in a study in which a daytime ambulatory BP <130 mmHg systolic and 80 mmHg identified WCH subjects in whom cardiovascular risk was low and not dissimilar from true normotension.96 (Figure 8). A complementary explanation, however, is that office BP is by no means devoid of a prognostic value, vis-à-vis ambulatory or home BP measurements. This is not at odds with the increased risk seen in patients with selective ambulatory (or masked) hypertension; because in these individuals, office BP, although within the normal range, is higher than in true normotension.96 (Figure 8, right panel). It is further in line with the evidence from the PAMELA study that (1) in WCH office BP independently predicted the development of high cardiovascular risk conditions such as sustained hypertension or diabetes mellitus when tested by multivariable analysisootnote{96,107} and (2) in both WCH and the general population there was a progressive increase in the risk of cardiovascular mortality from a condition of office, ambulatory, and home BP normality to the conditions in which 1, 2, or all 3 pressures were elevated.96 (Figure 9). Taken together these observations suggest that the prognostic information provided by office, ambulatory, and home BP may be complementary, and that all 3 pressures contribute to the level of total cardiovascular risk. They also support a larger use of both office and out-of-office BP measurements in clinical practice. This is at present recommended by guidelines whenever physicians suspect the existence of a WCH or masked hypertension. However, it is further recommended, however, for the identification of other phenomena from which appropriate treatment decisions depend, such as (1) considerable variability of office BP over the same or different visits; (2) daily life hypotensive episodes, particularly in the elderly or in patients with diabetes mellitus; and (3) preeclampsia, sleep apnoea, and true resistant hypertension.

**Burning Questions**

In addition to the problems mentioned in the previous subsections, several burning questions on the prognostic value of ambulatory BP await scientific clarification. The first question is that of sustained hypertension but nevertheless greater than that of individuals with in- and out-of-office BP normality.

This might be explained by the fact that in WCH the normal ambulatory or home BP values are several mmHg higher than in true normotension.96 (Figure 8). A complementary explanation, however, is that office BP is by no means devoid of a prognostic value, vis-à-vis ambulatory or home BP measurements.

A complementary explanation, however, is that office BP is by no means devoid of a prognostic value, vis-à-vis ambulatory or home BP measurements. This is not at odds with the increased risk seen in patients with selective ambulatory (or masked) hypertension; because in these individuals, office BP, although within the normal range, is higher than in true normotension (Figure 8, right panel). It is further in line with the evidence from the PAMELA study that (1) in WCH office BP independently predicted the development of high cardiovascular risk conditions such as sustained hypertension or diabetes mellitus when tested by multivariable analysis and (2) in both WCH and the general population there was a progressive increase in the risk of cardiovascular mortality from a condition of office, ambulatory, and home BP normality to the conditions in which 1, 2, or all 3 pressures were elevated. (Figure 9). Taken together these observations suggest that the prognostic information provided by office, ambulatory, and home BP may be complementary, and that all 3 pressures contribute to the level of total cardiovascular risk. They also support a larger use of both office and out-of-office BP measurements in clinical practice. This is at present recommended by guidelines whenever physicians suspect the existence of a WCH or masked hypertension. It is further recommended, however, for the identification of other phenomena from which appropriate treatment decisions depend, such as (1) considerable variability of office BP over the same or different visits; (2) daily life hypotensive episodes, particularly in the elderly or in patients with diabetes mellitus; and (3) preeclampsia, sleep apnoea, and true resistant hypertension.

**Figure 8.** Office, 24-hour mean and home systolic blood pressure (SBP) values in true normotensives (NT), white coat hypertensives (WCH), and masked hypertensive (HT) individuals. The horizontal dashed lines refer to upper limit of normality for the 3 pressures. Figure created with data derived from Mancia et al.96
whether addition of ambulatory BP to office BP measurements substantially improves the accuracy of cardiovascular risk estimates, thereby justifying the increased complexity and cost involved in its routine implementation. To be addressed, this will need a large population study in which office and ambulatory BP are routinely measured and subjects are followed up for several years to collect enough cardiovascular events. To date, office and out-of-office (ambulatory and home) BP have been conjunctively measured in all individuals of a general population in the PAMELA study, which has shown that addition of ambulatory and home to office BP increases the area of the receiver operating characteristic mortality curves to a significant but only modest degree. Confirmation by other studies is needed because in the PAMELA study only a relatively small number of events was available, limiting its statistical power.

Two other burning questions are whether addition of ambulatory (and home) BP to office BP (1) improves the estimate of patient protection by antihypertensive treatment and (2) guiding treatment by both office and ambulatory BP leads to a greater reduction of cardiovascular or renal events compared with treatment guidance by office BP alone. In a study performed years ago, the regression of echocardiographic left ventricular hypertrophy seen in hypertensive patients during a 1-year treatment period was found to be more closely associated with the reduction in ambulatory than the reduction in office BP.

Regrettably, however, except for 1 study, ambulatory BP has never been systematically measured in outcome trials on hypertension in which this information has been only collected in small subgroups selected in a nonrandomized fashion. Furthermore, ambulatory BP substudies from outcome-based trials have usually measured ambulatory BP once or twice during the on-treatment years (sometimes with no baseline ambulatory data) which means that the on-treatment ambulatory BP values corresponding to the office BP targets have also remained largely unknown. This represents a serious limitation to the use of ambulatory BP in the routine management of hypertension.

Finally, no information is available on the cardiovascular effects of antihypertensive treatment in masked hypertension, whereas in WCH data are limited to the observation that in these patients (1) the elevated office BP can be easily and markedly reduced by drug treatment, whereas this does not occur for ambulatory BP which shows over the years a trend to a progressive small increase and (2) in elderly patients with a much greater increase of office than of ambulatory systolic BP antihypertensive treatment did not significantly reduce cardiovascular events compared with placebo, whereas it did so in patients in whom both office and ambulatory systolic BP values were clearly elevated. The latter results, however, lacked statistical power, which calls for the question to be addressed by a future large randomized trial. This will have a great practical importance because WCH may represent 30% to 40% of the entire hypertensive population.

Disclosures

None.

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Gender-specific cardiovascular adaptation due to circadian blood pressure variations. Dippers and nondippers.


