Prognostic Value of Ambulatory Blood Pressure
Current Evidence and Clinical Implications

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Abstract—This article is a critical review of the available evidence on the prognostic value of ambulatory blood pressure (ABP). Several event-based cohort studies have shown that ABP improves cardiovascular risk stratification over and beyond traditional risk factors, including office BP. Most of these studies have been conducted in subjects with essential hypertension who were untreated at the time of execution of ABP monitoring; other studies have been conducted in subjects who were poorly controlled with treatment or in the general population. In these studies, ABP was examined as a continuous variable or with operational risk categories. Cardiovascular risk showed a direct and independent association with the observed ABP (systolic, diastolic, and pulse) and an inverse association with the degree of BP reduction from day to night. Cardiovascular risk was also directly associated with the difference between the observed value of ABP and that predicted from the office BP. White-coat hypertension versus ambulatory hypertension and dippers versus nondippers are 2 classifications based on arbitrary operational risk categories. A blunted or absent BP reduction from day to night, defined with ABP as a continuous variable or with operational thresholds, was also associated with a worse outcome regardless of the average value of ABP during the 24 hours. Overall, these studies indicate that ABP monitoring is particularly valuable to refine cardiovascular risk stratification in untreated subjects with office hypertension and in those with resistant hypertension. Intervention studies targeted at ABP are now needed. **(*Hypertension*. 2000;35:844-851.)**

Key Words: hypertension, arterial ■ hypertension, essential ■ hypertension, white-coat ■ blood pressure monitoring ■ stroke ■ myocardial infarction

In the past decade, there has been an explosive growth of ambulatory blood pressure (ABP) monitoring for research and clinical purposes.[1,2] Several outcome studies have been published, particularly during the past few years.[1–23] These studies have been conducted in the general population[19–21] or in hypertensive subjects, who were either untreated[3–14,16,22] or treated[15,17,18] at the time of ABP monitoring. The general result of these studies was that the difference in the cardiovascular (CV) disease risk between categories generated by 1 session of ABP monitoring was greater than the risk difference between categories generated by 1 or a few standard office measurements of blood pressure (BP). The Table provides an overview of full-length event-based prognostic studies on ABP conducted by several independent groups. Because most groups produced several reports on partially overlapping populations, each group is represented in the Table with its largest contribution. Moreover, the survival analyses of large studies, including the Cornell study,[13] Belgian study,[24] OvA study,[25] ELSA study,[26] and INSIGHT study,[27] are expected in the near future.

The purpose of this article was to review available evidence in regard to the prognostic value of ABP with the main aim of drawing useful clinical information to refine CV risk stratification. The prognostic value of ABP is examined with the approaches reported later.

ABP as a Continuous Variable

ABP has been analyzed as a continuous variable in some reports from the Ohasama study,[19,20] a general population study conducted in a Japanese rural area on ambulant subjects aged ≥20 years. After adjustment for age, gender, smoking status, baseline office BP, and the use of antihypertensive drugs, the mortality risk during a follow-up period of ≈5 years was increased in the highest quintile of the distribution of average 24-hour systolic BP, whereas no independent association was detected between office BP and mortality rates.[21] There was a U-shaped relationship between the average 24-hour BP, both systolic and diastolic, and CV mortality rates,[20] which was interpreted as a possible expression of the link between low BP levels and various morbid conditions in the general population. This study was the first to address the prognostic value of ABP in the general population. A potential limitation was the lack of statistical adjustment for diabetes and serum cholesterol level.

Another relevant study is that by Redon et al.[18] In this study, 86 patients with poorly controlled hypertension, defined as an office diastolic BP of >100 mm Hg despite

Received October 4, 1999; first decision October 22, 1999; revision accepted November 5, 1999.
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Event-Based Cohort Studies With ABP Monitoring: Contributions by Different Centers

Reference	Year	No. of Subjects	Type of Population	Follow-up, y	Total Events, n	Fatal Events, n
Full papers						
Perloff et al[3]	1983	1076	RPH, U	5	153	75
Zweiker et al[15]	1994	116	RPH, T	3	5	3
Ohkubo et al[20]	1997	1542	GP, U, T	5.1	NR	93
Nakano et al[23]	1998	325	Type 2 D	4.0	76	31
Redon et al[18]	1998	86	RPH, T	4	21	NR
Yamamoto et al[17]	1998	105	RPS, T, U	3.2	15	NR
Khattar et al[14]	1998	479	RPH, U	9.1	98	38
Verdecchia et al[10]	1998	2010	RPH, U	3.8	200	36
Staessen et al[16]	1999	808	RPH, U	4.4	98	68

RPH indicates referred patients with hypertension; GP, general population; RPS, referred patients with stroke; RPHE, referred patients on hemodialysis; U, untreated, T, treated; D, diabetes, and NR, not reported.

treatment with ≥3 drugs, including a diuretic, underwent 24-hour ABP monitoring. During a mean follow-up period of 4 years, 21 patients had a first CV event. After control for age, gender, smoking, left ventricular (LV) hypertrophy, and office BP, the event rate was significantly higher ($P<0.02$) in the upper tertile (13.6 events per 100 patient-years) than in the middle (9.5 events per 100 patient-years) and lowest (2.2 events per 100 patient-years) tertiles of daytime diastolic BP. Despite the small sample size and the lack of statistical adjustment for serum cholesterol level and family history of premature coronary heart disease, this study was the first to demonstrate the prognostic value of ABP in patients with resistant hypertension. According to this study, an average daytime diastolic BP of ≥88 mm Hg in a subject with an office diastolic BP of >100 mm Hg despite treatment with ≥3 drugs should be considered an adverse prognostic marker. Of note, resistant hypertension has been included as an established indication to ABP monitoring in both the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in their sixth report (JNC VI)[28] and the World Health Organization–International Society of Hypertension (WHO/ISH)[29] guidelines.

ABP has also been examined as a continuous variable in the setting of the Systolic Hypertension in Europe (Syst-Eur) study.[16] Of 808 patients with isolated systolic hypertension and ABP monitoring performed at the time of randomization, 98 developed a major CV event during a median follow-up period of 4.4 years. After adjustment for age, gender, office BP, active treatment, previous events, cigarette smoking, and residence in western Europe, the average nighttime systolic BP was a significant predictor of total, cardiac, and cerebrovascular events, whereas the average daytime BP did not yield statistical significance. For every 10-mm Hg increase in nighttime systolic BP, the hazard rate for cerebrovascular events was 1.20 (95% CI 1.08 to 1.35), whereas that for cardiac and cerebrovascular events was 1.16 (95% CI 1.02 to 1.33) and 1.31 (95% CI 1.06 to 1.62), respectively. In the placebo group, the night/day ratio of systolic ABP was an independent prognostic marker even after adjustment for the average 24-hour ABP. In this study, the same CV risk was predicted by systolic BP levels of 160 mm Hg (office BP), 142 mm Hg (average 24-hour ABP), 145 mm Hg (average daytime ABP), and 132 mm Hg (average nighttime ABP).[16]

Observed Versus Predicted ABP

If office BP versus the average daytime ABP is plotted, it is apparent that for any given value of office BP, the observed ABP is seldom that predicted with a linear regression equation, whereas it is most often higher or lower than predicted. In the landmark cohort study by Perloff et al,[3,4] the risk of CV events was significantly higher in the subjects with higher-than-predicted ABP than in those with lower-than-predicted ABP, particularly in the subjects with stage I hypertension. Although limited by the lack of a normotensive control group, nocturnal BP monitoring, and statistical adjustment for serum cholesterol level and cigarette smoking, this study provided the first consistent evidence of the prognostic value of noninvasive ABP monitoring and opened the way toward greater use of this diagnostic technology. It is important to note that the subjects with lower-than-predicted ABP do not have a "normal" ABP; hence, their CV risk should not be considered analogous to that of clinically normotensive subjects. Consequently, the 2 concepts of lower-than-predicted ABP and white-coat hypertension (WCH) (see later) must be kept separate. On the other side, in the subjects with higher-than-predicted ABP, the excess CV risk would remain undetected with office BP.

White-Coat Hypertension

WCH, which is also referred to as "office hypertension" or "isolated clinic hypertension,"[29] is generally defined as a persistently elevated office BP in the presence of a normal BP outside the office.[30] Although the usual definition of elevated office BP is not debated (≥140 mm Hg systolic, 90 mm Hg diastolic, or both),[28,29] there is controversy about the definition of normal BP outside the office. It is not easy to find 2 studies that used the same definition of WCH based on results of ABP monitoring.[30–48] The definition was based on both systolic and diastolic BP values in some studies[30–33,35,36,38,41–48] and solely on diastolic values in others[37,39,40]; some studies used the average ABP during the day,[30,31,35–38,40–44,48] and others used the average 24-hour ABP.[33,34,39,45,47] Still others added a measure of the

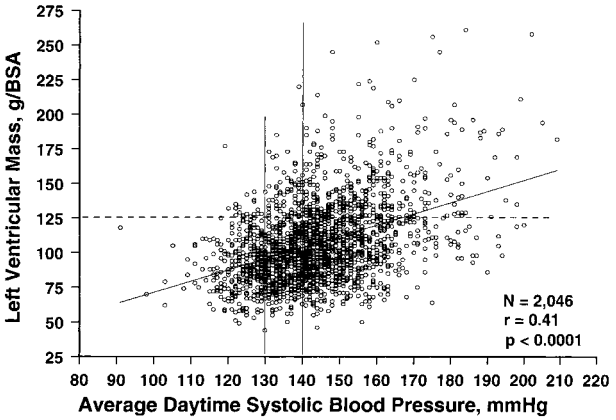

Figure 1. Association between average daytime ABP and LV mass at echocardiography in 2046 untreated subjects with essential hypertension. BSA indicates body surface area. (From Verdecchia et al[49] with permission.)

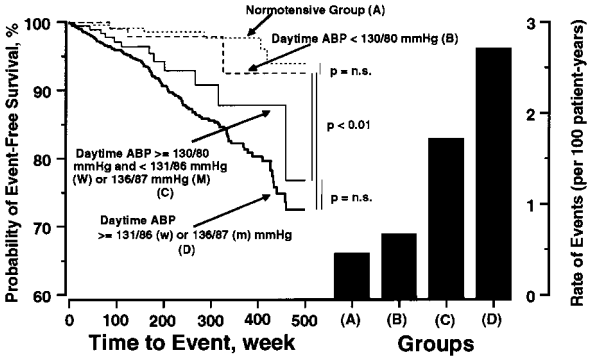

Figure 2. Rate of major CV morbid events in a normotensive group (A), 2 groups with WCH defined with a restrictive (B) or liberal (C) criterion, and a group with ambulatory hypertension (D). (From Verdecchia et al[22] with permission.)

office BP−ABP difference in the definition.[39] The upper reference limits of ABP used to define WCH differed across these studies; such differences might seem small and clinically unimportant, but the prevalence of WCH and LV mass on echocardiography increased markedly when moving from more restrictive (lower) to more liberal (higher) limits of ABP normalcy over a relatively narrow range.[36] Figure 1[49] shows that the prevalence of LV hypertrophy, virtually absent at <120 mm Hg and very low at <130 mm Hg (6%), increases to 10.5% when the limit is set to 140 mm Hg. Thus, modest swings over a narrow range of presumably normal or nearly normal ABP may result in remarkable differences in the prevalence of subjects with increased LV mass and, because of its established adverse prognostic value,[5,50–52] with increased CV risk.

To investigate the prognostic significance of WCH, in the setting of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study,[5] we followed for up to 7.5 years 1187 adults with essential hypertension and 205 healthy normotensive control subjects in whom off-therapy 24-hour ABP monitoring had been carried out at entry. The prevalence of WCH was 19.2%. The rate of combined fatal and nonfatal CV events (per 100 patient-years) was 0.47 in the normotensive group, 0.49 in the group with WCH, 1.79 in dippers (see later) with ambulatory hypertension, and 4.99 in nondippers with ambulatory hypertension. CV morbidity rates did not differ between the normotensive group and the group with WCH in a multivariate analysis ($P=0.83$). These results showed for the first time that CV morbidity rates are lower for WCH than for ambulatory hypertension and are not dissimilar between WCH and clinical normotension. In a larger analysis of the PIUMA database,[22] the subgroup with WCH was divided into 2 subsets with an average daytime ABP of <130/80 mm Hg or with intermediate values between 130/80 mm Hg and 131/86 mm Hg in women or 136/87 mm Hg in men. Figure 2 shows that the differences in event-free survival rates between the normotensive group and the group with WCH as defined more restrictively were not statistically significant, whereas the differences between the normotensive group and the WCH group as defined more liberally were significant. These data suggest that a daytime ABP of <130 mm Hg systolic and 80 mm Hg diastolic may be defined as optimum to identify WCH subjects at very low CV risk and not dissimilar from clinically normotensive subjects.

A document issued by the American Society of Hypertension[1] suggests the use of similarly restrictive upper limits to define normalcy of ABP (ie, average daytime BP <135 mm Hg systolic and <85 mm Hg diastolic). Furthermore, the results of the PAMELA study,[53] a cross-sectional general population study, indicate upper reference limits of daytime ABP of 129 to 132 mm Hg systolic and 80 to 85 mm Hg diastolic in men and of 125 to 129 mm Hg systolic and 80 to 82 mm Hg diastolic in women. These values correspond to an office BP of 140/90 mm Hg.

Khattar et al[14] recently completed a follow-up study of 479 subjects with essential hypertension who underwent 24-hour intra-arterial ABP monitoring before therapy. Intra-arterial BP monitoring is the gold standard for BP measurement, although not suitable for use in general clinical practice. The prevalence of WCH, defined as an average 24-hour ABP of <140/90 mm Hg, was 26%. During a follow-up period of 9 years, the rate of CV morbid events was 1.32 per 100 patient-years in the WCH group and 2.56 per 100 patient-years in the ambulatory hypertension group. These differences were significant after adjustment for age, gender, race, and smoking, whereas office BP did not yield statistical significance. In this study, the definition of WCH may not be comparable with that used in noninvasive studies because intra-arterial ABP averages may be higher than those resulting from noninvasive monitoring.[54] This study was the first to demonstrate, with intra-arterial ABP monitoring, the lesser CV risk in the subjects with WCH than in those with higher ABP. Unfortunately, a normotensive control group could not be included because of ethical reasons.

For now, it is reasonable to consider the possibility that antihypertensive drug treatment may be unnecessary in many subjects with WCH.[55] It is worth noting, however, that some of the subjects with WCH may be at an increased CV risk because of concomitant risk factors such as diabetes, cigarette smoking, or elevated cholesterol levels. Withholding antihypertensive drug treatment in these subjects on the basis of a "normal" ABP in the setting of a high office BP may be

problematical in the absence of evidence regarding the safety of such intervention. Thus, randomized intervention studies are urgently needed in subjects with WCH to compare a regimen based on lifestyle measures without drugs with a standard regimen consisting of lifestyle measures with the possible addition of drugs according to current recommendations[28,29] based on office BP. Unfortunately, these studies are unlikely to be supported by institutions other than government agencies or scientific or insurance societies.

On the basis of current evidence, we suggest a temporary verdict of innocent and a treatment based on lifestyle measures in this low-risk stratum of subjects with essential hypertension under the conditions of a correct definition, the absence of important comorbid conditions, and adequate follow-up.[49] A correct definition includes an average daytime ABP of <135 mm Hg systolic and 85 mm Hg diastolic, whereas levels of <130 mm Hg systolic and 80 mm Hg diastolic may be defined as optimum.

White-Coat Effect

The measurement of BP in the physician's office may trigger an alerting reaction and a rise in BP.[56,57] Mancia et al[58,59] have shown that the rise in intra-arterial BP during the visit is, on average, 27/14 mm Hg; it is maximal during the first 4 minutes of the visit, disappears within ≈10 minutes, and persists over several visits. The transient rise in BP from before to during the visit is usually defined as "white-coat effect" or "white-coat phenomenon," whereas the coexistence of persistently high office BP with normal ABP, regardless of the extent of the white-coat effect, is often referred to as WCH. From a practical standpoint, it is worth noting that the white-coat effect is a measure of BP change from before to during the visit,[58,59] whereas WCH is an operative definition of clinically hypertensive subjects at a low potential risk because of apparently normal mean BP levels during daily life.[30,60] A reliable estimate of the white-coat effect may be carried out through intra-arterial[58,59] or noninvasive[61] techniques, with beat-by-beat measurement of the BP rise from immediately before to during the visit. The white-coat effect has also been estimated as the difference between office BP and average daytime ABP, based on the assumption that average daytime ABP corresponds to the BP immediately before the visit. However, there seems to be no association between the BP rise from before to during the visit, as determined on a beat-to-beat basis with the Finapres method, and the difference between office BP and daytime ABP.[61] From a prognostic standpoint, in the setting of the PIUMA study, the rates of both total and fatal CV disease events did not show any association with the office BP−ABP difference.[8] These data indicate that the office BP−ABP difference, taken as a measure of the white-coat effect, is not a predictor of CV morbidity and mortality rates in subjects with essential hypertension.

Day−Night BP Changes

Intra-arterial studies with beat-to-beat recording in ambulant subjects showed that BP falls by ≈20% to 25% from daytime to nighttime.[62,63] In the past years, 24-hour noninvasive ABP monitoring has been widely used to investigate the diurnal BP changes associated with the sleep-wake cycle.[1,2] Day and night have been defined as the waking and sleeping periods from the patient's diary or through arbitrarily defined fixed time intervals, that are either wide (usually from 6 AM to 10 PM for day and from 10 PM to 6 AM for night) or narrow (from 10 AM to 8 PM for day and from midnight to 6 AM for night). The use of narrow fixed-clock intervals excludes the morning and evening transitional periods, during which a variable proportion of subjects are actually awake or asleep, and seems to be preferable to wide fixed time intervals because it provides a more accurate estimate of the actual BP values during sleep and wakefulness, at least in subjects going to bed and arising in reasonably well-defined time intervals.[64–66] An important support for the use of noninvasive technology to assess the day−night BP changes was the demonstration that intra-arterial 24-hour BP profiles are similar in the absence and presence of concomitant noninvasive BP monitoring.[67,68]

The dippers/nondippers classification was first introduced by O'Brien et al,[69] who reported a more frequent history of stroke in nondippers than in dippers. Such classification is based on the hypothesis that target organ damage and prognosis are worse when the BP load is persistent throughout the 24 hours than when it is limited to the daytime hours. Generally, nondippers are defined by a reduction in BP by less than a given percentage from day to night, and the subjects out of this definition are classified as dippers. The threshold values for classification may range from 10%,[70] or 10/5 mm Hg,[69] to 0% (ie, no reduction in BP from day to night or a higher BP during the night than during the day). The prevalence of nondippers varied among different studies depending on several factors, including the definition of daytime and nighttime and the division line between dippers and nondippers.[71] Like all categorizations of continuous variables, the dipper/nondipper classification has been criticized because it implies an arbitrary dichotomization of a continuous variable (ie, the day−night difference in BP) and because the definitions of daytime and nighttime and that of the partition line between dippers and nondippers are arbitrary. However, such classification appears useful from a clinical standpoint because several reports from independent centers showed that not only LV hypertrophy[70,72–75] but also silent cerebrovascular disease,[76,77] microalbuminuria,[78,79] and progression of renal damage[80] were greater in subjects with a blunted or an abolished fall in BP from day to night than in those with a normal day−night BP difference. A meta-analysis by Fagard et al[81] suggests that the day−night BP difference accounts for no more than 15% of LV mass.

In the PIUMA study, a greater LV mass in nondippers than in dippers was found only in those subjects with abnormally increased ABP values, not in the normotensive subjects or in subjects with WCH.[82] Thus, a blunted day−night BP fall may be expected to be harmful only when the average level of ABP is abnormal. Other groups have shown that not only LV mass but also peripheral arterial changes detected by ultrasonography[72] and cerebral lacunae detected with magnetic resonance imaging,[76,77] are greater in nondippers than in dippers. Lacunae showed a J-shaped profile, with an increase of lacunae in both nondippers and extreme dippers compared with dippers, which was interpreted as a possible result of

nocturnal hypotension with consequent ischemia due to defective autoregulation of cerebral blood flow.[77] The prognostic implications of this finding are still unknown.

When dippers and nondippers are compared, it is important to adjust for possible imbalances between the groups in the average 24-hour ABP. If the 2 groups are matched by daytime ABP only, the average 24-hour values will be higher in nondippers than in dippers. In the PIUMA study,[5] hypertensive women with a nondipping pattern at the baseline evaluation had a higher CV morbidity rate during follow-up than dippers, and this difference remained significant after control for traditional risk markers. A nonsignificant trend in the same direction was found in men.[5] In a recent analysis of a larger PIUMA sample,[6] we examined the relation between CV morbidity rates and night/day BP ratio, a continuous measure of the nocturnal BP reduction. In such an analysis, the rate of CV events significantly increased in both genders with the night/day ratio of systolic BP even after adjustment for age, diabetes, and 24-hour systolic ABP.[6]

The adverse prognostic significance of a blunted day−night rhythm of ABP was confirmed in other studies. In the Ohasama study, Ohkubo et al[21] found an increased CV mortality rate in nondippers (relative risk 2.56, $P=0.02$) and inverted dippers (relative risk 3.69, $P=0.004$) compared with dippers. A limitation of this study was the lack of statistical adjustment for the potential influence of diabetes and serum cholesterol level. Another study from Japan showed a higher risk of CV events in nondippers than in dippers among subjects with type 2 diabetes.[23] In a small study carried out in 116 treated hypertensive subjects followed for an average of 31 months, Zweiker et al[15] noted a significantly ($P<0.001$) higher rate of CV complications in nondippers (4 events in 29 subjects) than in dippers (1 event in 87 subjects). In a study from Japan,[17] 105 patients with symptomatic lacunar infarcts underwent 24-hour ABP monitoring. Follow-up lasted an average of 3.2 years. The degree of ABP reduction from day to night at the baseline assessment was significantly ($P<0.01$) smaller in the group with subsequent cerebrovascular events (1.3% for systolic BP, 3.3% for diastolic BP) than in the group with no future events and no development of silent lacunae (7.2% for systolic BP, 10.4% for diastolic BP). In the analysis of the Syst-Eur study mentioned earlier, the night/day ratio of systolic ABP was an independent predictor of CV events in the subset randomized to placebo.[16] For every 10% higher night/day ratio of systolic BP, the hazard rate for total CV events was 1.41 (95% CI 1.03 to 1.94, $P=0.03$) after control for many confounders, including 24-hour ABP.[16]

These findings indicate that the assessment of day−night BP changes detected with noninvasive ABP monitoring is important in hypertensive subjects because it allows an improvement in CV risk stratification above office BP and other traditional risk markers. Obviously, 24-hour ABP monitoring is the only practical way to assess the day−night rhythm of BP.

BP Variability

In some studies with intra-arterial[83] and noninvasive[74] ABP monitoring, frequency and severity of target organ damage were greater in subjects with high BP variability than in those with low variability. In the PIUMA study, for any level of 24-hour systolic BP, hypertensive subjects were classified at low or high BP variability according to their standard deviation of daytime and nighttime systolic BP below or above the median. LV mass at echocardiography did not differ between the groups at low versus those at high systolic BP variability.[84] We also used the PIUMA database to investigate the prognostic value of ultradian BP variability.[7] In that study, the rate of major CV morbid events was higher in the subjects with standard deviation of daytime or nighttime systolic BP above the group mean than in those with standard deviation below the group mean. However, this difference did not hold in a Cox multivariate analysis after adjustment for age, diabetes, previous CV events, and ABP.[7] Thus, the adverse impact of increased BP variability was largely spurious and resulted from the confounding effect of age, BP, diabetes mellitus, and previous CV morbid events, all potential markers of increased vascular damage and reduced baroceptor sensitivity.[85] The potential prognostic value of invasive and noninvasive beat-to-beat techniques for the assessment of BP variability remains to be determined.

Ambulatory Heart Rate

Heart rate measured at rest in the physician's office is a recognized predictor of CV complications.[86,87] However, the alerting reaction to visit evokes not only a rise in BP but also a variable tachycardic effect.[58,59] Consequently, we analyzed the PIUMA database[9] to investigate the association among heart rate, both office and ambulatory, with CV and non-CV events. For an average of 3.6 years, we followed 1942 initially untreated and uncomplicated subjects with essential hypertension, and all subjects underwent simultaneous assessment of ABP and heart rate, with 1 reading every 15 minutes for 24 hours. Unexpectedly, there was no association between all-cause mortality and office, average 24-hour, daytime, and nighttime heart rate. However, the subjects who subsequently died showed a blunted reduction in heart rate from day to night at the baseline examination. After adjustment for age, diabetes, and average 24-hour systolic BP, for each 10% reduction in the heart rate from day to night, the relative risk of death was 1.30 (95% CI 1.02 to 1.65, $P=0.04$).

Ambulatory Pulse Pressure

A significant association has been noted in several studies between pulse pressure (PP) and the subsequent rate of CV morbid events, and such an association was independent of systolic and diastolic BPs.[5,88–91] In a previous study from our laboratory, such an association was also independent of LV mass at echocardiography and WCH.[5] However, PP may be affected by the alerting reaction evoked by the clinical visit. Mancia et al[58,59] showed that the rise in intra-arterial systolic BP is greater (4 to 75 mm Hg, mean 27 mm Hg) than that of diastolic BP (1 to 36 mm Hg, mean 15 mm Hg). This implies an average rise in PP of ≈12 mm Hg from before to during the visit. Office PP thus may overestimate the usual levels of PP. To investigate the prognostic value of ambulatory PP, we studied 2010 initially untreated and uncomplicated subjects

with essential hypertension from the PIUMA database.[10] The rates of total CV events (per 100 person-years) in the 3 tertiles of the distribution of average 24-hour PP were 1.19, 1.81, and 4.92, and those of fatal events were 0.11, 0.17, and 1.23 (both $P<0.01$, log-rank test). After control for concomitant risk markers, including WCH and the day−night BP change, survival data were better fitted by the model containing ambulatory PP than by that containing office PP. For any given level of office PP, CV morbidity and mortality rates markedly increased with average 24-hour ambulatory PP. These data suggest that the alerting reaction to office BP measurement may weaken the relation between PP and CV risk. Consequently, ambulatory PP appears to provide a more precise estimate of risk. Prospective intervention trials are now needed to assess whether PP is equivalent or superior to systolic and diastolic BPs as a guide for antihypertensive therapy.

Indications for ABP Monitoring Based on Prognostic Studies

Indications for ABP monitoring are still unsettled. Both the JNC VI Committee[28] and the WHO/ISH Committee[29] provided a list of general situations in which ABP monitoring might be useful. According to the JNC VI document,[28] these conditions are "suspected WCH," "episodic hypertension," "hypotensive symptoms with antihypertensive medications," "autonomic dysfunction," and "apparent drug resistance." According to the WHO/ISH document,[29] these conditions include "office hypertension in subjects with low CV risk," "unusual variability of BP over the same or different visits," "symptoms suggesting hypotensive episodes," and "hypertension resistant to drug treatment." However, as shown in the Table, the available evidence supporting the prognostic value of ABP is remarkable and based mostly on outcome cohort studies in which the qualifying ABP monitoring had been carried out in untreated subjects with essential hypertension.[3–14,16,22] Therefore, a grade B recommendation with a 2b level of evidence[92] would be that of considering the clinical usefulness of ABP monitoring for the refinement of CV risk stratification above and beyond traditional risk markers in all untreated subjects with essential hypertension as well as in those with resistant hypertension despite the use of ≥3 drugs.[18] In contrast, there is no evidence that ABP improves CV risk stratification in most of the treated hypertensive subjects, particularly in those well controlled with therapy. The ongoing OvA study[25] will be able to provide a final answer to this point. From an operational standpoint, ABP could first identify a low-risk subset with "normal" mean levels of ABP (WCH). In the subjects with higher ABP (ambulatory hypertension), a nondipping pattern, generally defined by a reduction in systolic BP from day to night by <10%, as well as an average 24-hour PP of >53 mm Hg,[10] would identify a high-risk category. The remaining subjects would belong to an intermediate-risk category (Figure 3).

Perspectives

Several years ago, observational surveys identified office BP as a predictor of CV disease, thus justifying the execution of intervention studies targeted at office BP in patients with essential hypertension. The stage is now set for prospective intervention studies targeted at ABP within the 2 following general areas.

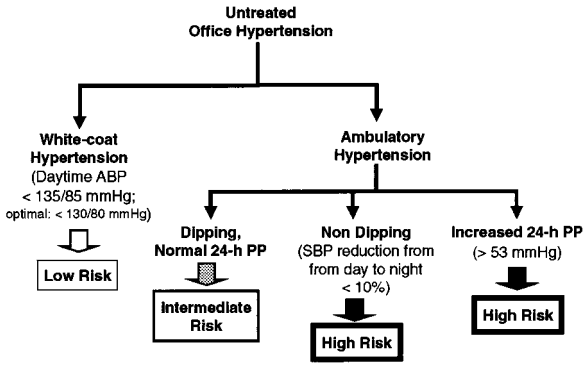

Figure 3. Operational approach for CV risk stratification on the basis of ABP in untreated subjects with essential hypertension.

(1) In low-risk subjects with WCH, there is a need to determine whether a standard management of hypertension based on office BP differs from a no-drug management in terms of the development of organ damage and, it is hoped, prognosis. The standard management would consist of lifestyle measures and drug treatment when indicated. The no-drug management would consist of lifestyle measures alone, with possible switch to drug treatment beyond predefined ethical thresholds.

(2) There is a need to determine whether a standard management of hypertension completely based on office BP without the execution of ABP monitoring differs, in terms of the development of organ damage and, it is hoped, prognosis, from a management targeted on the results of ABP monitoring.

These studies should also include cost-effectiveness analyses to test the hypothesis that ABP monitoring in the management of subjects with essential hypertension may lead to a net financial gain.[55]

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