

Review

Interpretation of Ambulatory Blood Pressure Monitoring for Risk Stratification in Hypertensive Patients: The ‘Ambulatory Does Prediction Valid (ADPV)’ Approach

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Abstract: Several outcome-based prospective investigations have provided solid data which support the prognostic value of 24 h ambulatory blood pressure over and beyond cardiovascular traditional risk factors. Average 24 h, daytime, and nighttime blood pressures are the principal components of the ambulatory blood pressure profile that have improved cardiovascular risk stratification beyond traditional risk factors. Furthermore, several additional ambulatory blood pressure measures have been investigated. The correct interpretation in clinical practice of ambulatory blood pressure monitoring needs a standardization of methods. Several algorithms for its clinical use have been proposed. Implementation of the results of ambulatory blood pressure monitoring in the management of individual subjects with the aim of improving risk stratification is challenging. We suggest that clinicians should focus attention on ambulatory blood pressure components which have been proven to act as the main independent predictors of outcome (average 24 h, daytime, and nighttime blood pressure, pulse pressure, dipping status, BP variability).

Keywords: hypertension; blood pressure; ambulatory blood pressure; ambulatory blood pressure monitoring; prognosis; epidemiology



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1. Introduction

Since diagnosis and clinical management of hypertension are based on blood pressure (BP) measurements taken in the physician’s office, most of the diagnostic and treatment recommendations issued by major hypertension guidelines are based on office BP [1,2]. Nonetheless, 24 h non-invasive ambulatory BP monitoring (ABPM) is increasingly used to refine cardiovascular risk stratification [3–10]. It is today well established that BP measured in the hospital or in the doctor’s office (‘office’ or ‘clinic’ BP) generally provides limited information on the real BP load and variability over the 24 h period. On the other hand, more frequent ambulatory BP measurements during the entire 24 h period can provide an accurate landscape of the real patient’s BP during usual daily activities and during sleep. As depicted in Figure 1, at any level of office BP, the observed ambulatory BP varies dramatically around the value predicted from the regression equation.

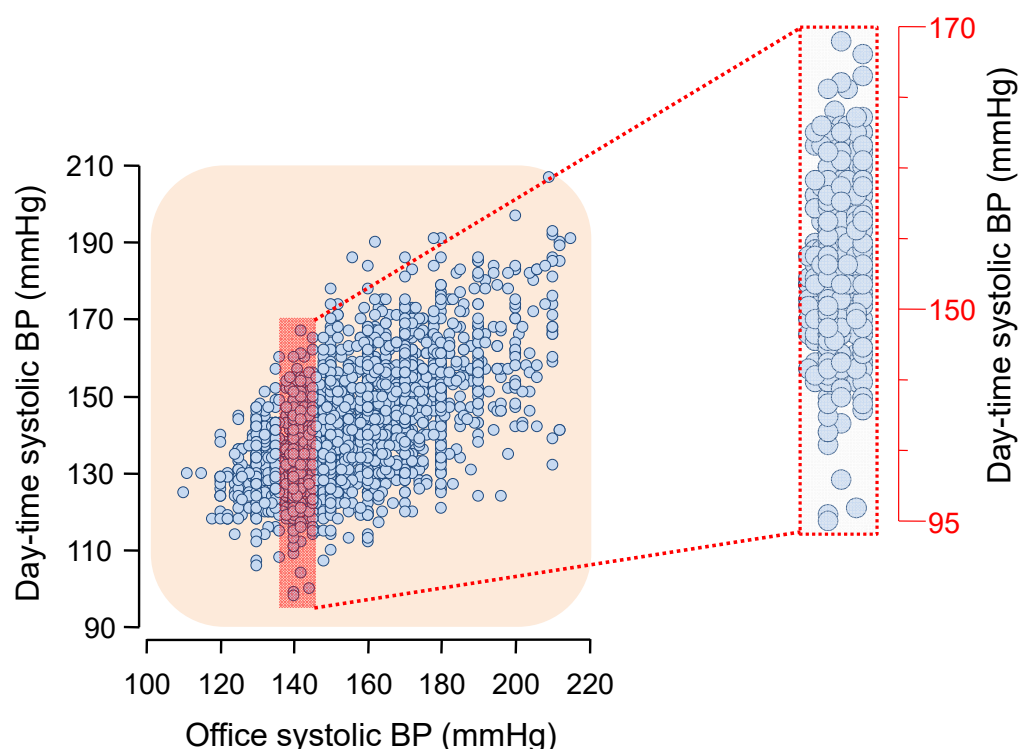


Figure 1. Association between ambulatory and office BP (see text for details). BP = blood pressure. Data from the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study.

The independent association between ambulatory BP, hypertensive target organ damage, and the risk of cardiovascular events in hypertensive patients (either treated or untreated) is now well established [3,4,11–13]. The main aim of our narrative review is to analyze the advantages of ambulatory BP over office BP in refining risk stratification and in predicting clinical outcomes in hypertension. We also discussed the most appropriate way of interpreting ambulatory BP profiles in the prognostic evaluation of patients with hypertension.

2. Average Ambulatory BP

ABPM enables clinicians to obtain a precise estimation of a patient's BP profile by measuring BP during daytime and nighttime periods [14]. Solid evidence from large longitudinal clinical studies supports the prognostic impact of average ambulatory BP over and beyond office-based BP [14].

Some landmark studies have addressed the independent prognostic value of average ambulatory BP. In the Ohasama study, ambulatory BP predicted the risk of cardiovascular mortality after adjustment for several potential confounders, including office BP [15]. An analysis of a Danish population demonstrated that average ambulatory daytime systolic BP was a stronger predictor of adverse outcomes independent of office-based systolic BP [16,17]. An analysis of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) study, conducted in 7030 subjects from Denmark, Belgium, Japan and Sweden [17], concluded that average daytime ambulatory BP was a stronger predictor for the risk of cardiovascular events than office-based BP measurement. In a fully-adjusted model which included both ambulatory and office BP, office BP was no longer statistically significant, while daytime systolic BP conversely remained strongly significant [17]. Similar results were documented in elderly subjects with elevated systolic and normal or low diastolic BP ('isolated systolic hypertension'). Ambulatory systolic BP proved to be a stronger predictor of cerebrovascular and cardiovascular events when compared with office BP [18]. Studies conducted in independent centers with similar experimental design provided similar results (Table 1).

Table 1. Landmark outcome-based studies which assessed the prognostic significance of ambulatory BP (see text for details). PIUMA = Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; OvA = Office Versus Ambulatory Blood Pressure; PAMELA = Pressioni Arteriose Monitorate E Loro Associazioni.

Study/Setting (N, Number of Patients)	Results	Ref.
Resistant hypertension (N = 86)	The cardiovascular event rate was significantly higher in the upper tertile than in the middle/lower tertiles of daytime diastolic BP.	[19]
PIUMA study; clinically hypertensive patients and normotensive controls (N = 2010)	The rate of major cardiovascular events was comparable in hypertensive patients with white coat hypertension and normotensive subjects (i.e., office BP < 140/90 mmHg). Among clinically hypertensive subjects it was higher in non-dippers than in dippers.	[20]
PIUMA study; clinically hypertensive patients and normotensive controls (N = 790)	The rate of major cardiovascular events was lower in hypertensive patients with ambulatory BP control (<135/85 mmHg: 0.71 events/100 person-years) than in uncontrolled patients (1.8 events/100 person-years). Ambulatory BP control, but not office BP control, was an independent predictor of a reduced risk of subsequent cardiovascular events.	[21]
OvA study; treated hypertensive patients (N = 1963)	In a multivariate model adjusted for several covariates, including office BP, average 24 h ambulatory BP was an independent predictor of major cardiovascular disease.	[22]
Dublin outcome study; patients referred for management of cardiovascular risk (N = 5292)	Ambulatory BP proved strongly superior to office BP in the prediction of cardiovascular mortality before and after allowances for confounders. In particular, elevated nighttime BP proved to be the most powerful independent prediction of poor outcomes.	[23]
PAMELA study; hypertensive patients (N = 2051)	Nighttime ambulatory BP was superior to daytime BP as a prognostic predictor.	[24]
Pierdomenico et al. (N = 738)	Patients with non-resistant and resistant masked uncontrolled hypertension are at increased risk of major cardiovascular events compared to subjects with controlled hypertension.	[25]

2.1. White Coat Hypertension

Numerous clinical studies and guidelines have defined white coat hypertension (WCH), also referred to as ‘isolated office hypertension’, as a phenotype characterized by hypertension detected by the doctor in his/her office in individuals with normal BP at home or during normal daily activities [26–29]. The prognostic significance of WCH has been investigated in many outcome-based studies. Some cohort and interventional studies showed that cardiovascular risk in subjects with WCH (a) is comparable to that of clinically normotensive subjects and (b) is consistently lower than in subjects with elevated ambulatory BP [17]. Other studies provided different results by showing that organ damage and risk of events are slightly increased in subjects with WCH than in clinically normotensive subjects [29,30].

In a study published in *The Lancet*, we subdivided hypertensive patients with WCH into two groups with pretty low (<130/80 mmHg) or intermediate (between 130/80 and 131/86 mmHg in women or 136/87 mmHg in men) daytime ambulatory BP. The difference in the risk of major cardiovascular events between clinically normotensive subjects and the hypertensive group with WCH defined restrictively was not statistically significant. Conversely, the differences between the normotensive group and the WCH group defined less restrictively were significant. In other words, these results suggest that a daytime ambulatory BP < 130/80 mmHg identifies hypertensive patients with WCH who are really at low cardiovascular risk. This analysis has been more recently replicated in a huger sample of 3174 patients with 376 major cardiovascular events over a mean follow-up period of 7 years. The analysis confirmed that the clinically normotensive group and the group of patients with WCH defined more restrictively (daytime BP < 130/80 mmHg) were comparable in terms of their risk of major cardiovascular disease. Conversely, the differences between the clinically normotensive group and the WCH group defined less restrictively achieved significance. Notably, these data have been confirmed in independent prospective studies [31,32] which included 1038 individuals with mild hypertension followed for an average of 4.5 years [31] and 958 elderly Japanese patients followed for an average of 3.5 years [32].

An international collaborative clinical study collected individual patient data from 4406 patients from four prospective cohort studies conducted in Italy, the United States, and Japan who were followed for a median of five years [10]. In a fully adjusted multi-variable model, the hazard ratio for stroke was 1.15 (0.61–2.16) in the WCH group and 2.01 (1.31–3.08) in the ambulatory hypertension group compared with the normotensive group [10]. Nonetheless, stroke risk increased in the WCH group over time and the Kaplan–Meier curve in the WCH group crossed that of the ambulatory hypertension group by approximately the ninth year of follow-up. Based on these data, we suggested that WCH might not be a fully benign condition for stroke in the very long term [10].

Consequently, hypertension guidelines suggest that subjects with WCH should be extensively investigated for concomitant risk factors and target organ damage in order to inform therapeutic decisions [1]. So far, there are no randomized studies comparing a ‘drug treatment’ with ‘no treatment’ in subjects with WCH in the absence of other indications for treatment [1].

2.2. Masked Hypertension

Over the years, several studies have addressed a new clinical phenotype with normal BP (i.e., <140/90 mmHg) in the doctor’s office and increased BP levels during usual daily activities outside the doctor’s office. Pickering defined this condition as ‘masked hypertension’ (MH). Clearly, the term MH underscores the concept that hypertension might not be diagnosed in these individuals on the basis of office BP measurements. Various factors are known to increase BP during usual daily life (alcohol, physical activity, diabetes, obesity, psychological stress, cigarette smoking, etc.) and these factors could thus raise BP out of the doctor’s office.

Several studies have shown that hypertensive organ damage is comparable between patients with MH and those with elevated BP during normal daily activities, despite the remarkable differences in office BP. From a prognostic standpoint, patients with MH showed a 1.5- to 3-fold higher risk of major cardiovascular disease than subjects with normotension, and their outcomes did not differ significantly from those of patients with elevated office and out-of-office BP [5,33–35]. Similarly, MH defined by self-measured home BP proved to have prognostic significance [5,36]. In a study conducted in 4939 treated hypertensive patients (mean age 70 years) followed for about 3 years, the cardiovascular disease rate was only 11.1/1000/year when office BP was <140/90 and self-measured BP at home was <135/85, while this rate was 30.6/1000/year in the presence of MH, defined by a home BP \geq 135/85 mmHg and an office BP < 140/90 [36].

In a meta-analysis, we evaluated the prognostic impact of MH defined by either ambulatory or self-measured BP [5]. We examined data from prospective studies, which included both normotensive and hypertensive subjects, either treated or untreated, and MH defined by ambulatory BP or self-measured BP [5]. We calculated the hazard ratio (HR) and 95% confidence interval (CI) for each study separately, and then derived the HR and 95% CI according to random-effects models [5]. Based on the aforementioned criteria, we identified eight clinical studies divided in two subgroups: (a) studies which investigated the prognosis of MH detected by ambulatory BP ($n = 6$) and (b) studies which investigated the prognostic impact of MH detected by self-measured BP ($n = 2$) [5]. The risk of major cardiovascular disease events was considerably higher in the subjects with MH than in the normotensive subjects, regardless of whether the definition of MH was based on self-measured BP (HR: 2.13; 95% CI: 1.35–3.35; $p = 0.001$) or 24 h ABPM (HR: 2.00; 95% CI: 1.54–2.60; $p < 0.001$) [5].

Overall, these data strongly suggest that MH should be considered an insidious and prognostically adverse condition that can be reliably diagnosed by self-measured BP and ambulatory BP. Antihypertensive treatment is advised in these subjects, although the associated outcome benefits are still undetermined. So far, there are no randomized outcome-based studies specifically designed to assess the prognostic impact of hypertensive treatment in subjects with MH.

Although average ambulatory BP (24 h, daytime, and nighttime BP) has been extensively investigated as a prognostic determinant in hypertension, other measures exist for describing different aspects of ambulatory readings. They include changes from day to night in BP, morning surges, pulse pressure (PP), and estimates of BP variability [37–45].

3. Day–Night BP Changes and Early Morning Rises in BP

It is now well established that there is a physiological decline in BP from the daytime to the nighttime window, with BP values tending to peak during the awake period and then falling to a nadir during the night [46,47]. In this context, ABPM is the best tool to investigate BP changes from day to night [48].

3.1. Dipping Status

The “dipper/non-dipper” classification was first introduced by O’Brien in 1988 on the basis of clinical observations of a more frequent history of stroke among subjects with absent or blunted BP decline from day to night [49].

Subjects with a day–night BP difference below a given value are usually referred to as ‘non-dippers’, and the remaining subjects are usually referred to as ‘dippers’. To date, the suggested values for this distinction range from 10% to 10/5 mmHg up to 0% (i.e., no reduction in BP from day to night or higher BP during the night than during the day) [50]. Furthermore, BP in some patients is actually higher during the night than during the day (Figure 2). This phenomenon is usually referred to as ‘reverse dipping’ and is associated with an adverse cardiovascular outcome [51].

After evidence of an association between “non-dipping” patterns and target organ damage (including left ventricular hypertrophy, microalbuminuria, angiographic coronary artery stenosis, and previous cerebrovascular events with or without cognitive dysfunction [41,49,52–54]), several outcome-based studies confirmed that a diminished nocturnal BP fall is associated with poor prognosis in hypertensive subjects [55], thereby refining cardiovascular risk stratification (Table 2) [8,56–59].

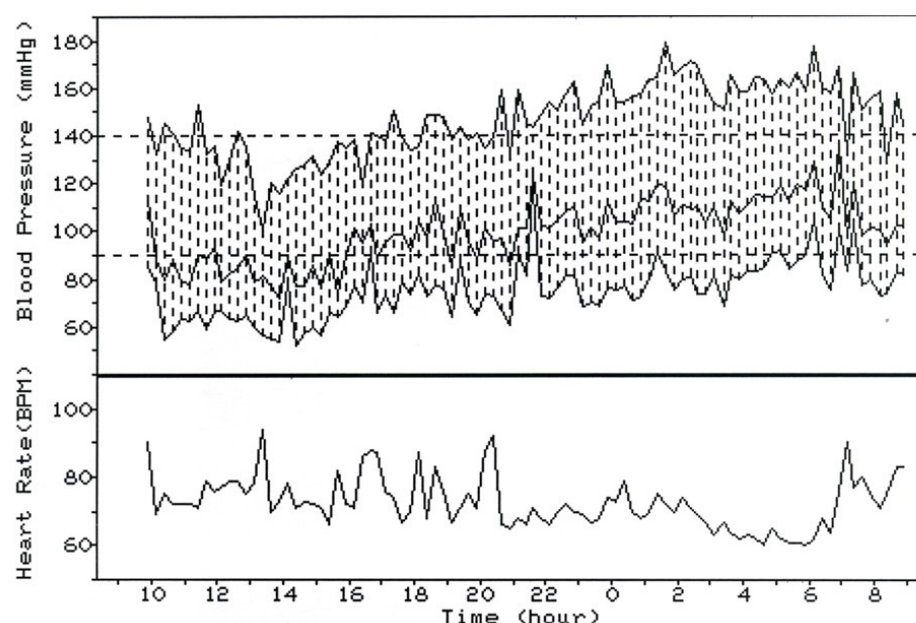


Figure 2. Higher BP during the night than during the day ('reverse dipper' or 'riser' profile) in a patient with chronic kidney disease. Data from the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study.

Table 2. Clinical studies assessing the prognostic value of non-dipping patterns (see text for details). PIUMA = Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; Syst-Eur = Systolic Hypertension in Europe.

Study (N, Number of Patients)	Results	Ref.
Yamamoto et al. (N = 105)	The day–night BP reduction was lower in patients with future cerebrovascular events than in those without.	[60]
Syst-Eur trial (N = 808)	At any level of 24 h ambulatory BP, the risk of major cardiovascular disease increased with the night-to-day ratio of systolic BP.	[18]
Ohkubo et al. (N = 1542)	The rate of cardiovascular mortality was higher in 'non-dippers' and 'reverse dippers' than in 'dippers'.	[61]
PIUMA study (N = 2934)	Regardless of the definition of day and night (i.e., fixed time intervals or based on a diary) the day–night BP changes are prognostically important.	[8]
PIUMA study (N = 2934)	The prognostic value of day–night BP drops is absent in patients who experience important alterations in the reported duration of sleep during nocturnal monitoring.	[7]

Several factors, including chronic kidney disease (CKD) and left ventricular hypertrophy (LVH), may influence the degree of BP fall from day to night. Consequently, the prognostic impact of the day–night BP fall could be influenced by CKD and LVH. In a recent analysis of the PIUMA study, the day–night BP fall remained a predictor of cardiovascular risk in the absence of data regarding CKD or LVH. However, somewhat unexpectedly, after adjustment for CKD (estimated glomerular filtration rate <60 mL/min or proteinuria) and LVH, the day–night BP fall was no longer significant for risk stratification in these patients [58]. These data strongly suggest that a non-dipping pattern is a sort of proxy

of hypertensive organ damage at renal or cardiac level [58]. The day–night BP fall did not improve the prognostic information provided by CKD or LVH. Interestingly, the independent competing models which included 24 h, daytime or nighttime BP combined with the day–night BP fall were equally informative for cardiovascular risk prediction. In other words, when clinical data on CKD and LVH are available, the day–night BP fall is of secondary clinical importance.

3.2. Early Morning BP Surge

More recently, some studies have analyzed the association between early morning BP surges and outcomes in hypertension. It is well known that myocardial infarction, stroke, and sudden cardiac death tend to cluster in the early morning, especially during the 4–6 h after awakening [51].

These observations support the hypothesis of a pathophysiological relationship between hemodynamic aberrations in the early morning (Figure 3) and vascular damage [62–65]. On the other hand, the hypothesis of an adverse prognostic significance of a blunted or reversed diurnal BP rhythm, demonstrated in several clinical studies, may be difficult to reconcile with the assumption that an excessive early morning rise in BP is also predictive of a worse outcome. Indeed, an exaggerated early morning rise in BP could be expected more frequently among dippers than non-dippers or reverse dippers. Unfortunately, most studies that have evaluated the morning BP surge have been conducted in relatively small cohorts of individuals with high BP who were untreated at the time of 24 h monitoring. The impact of antihypertensive treatment on the day–night BP fall and the early morning rise in BP could indeed be critical.

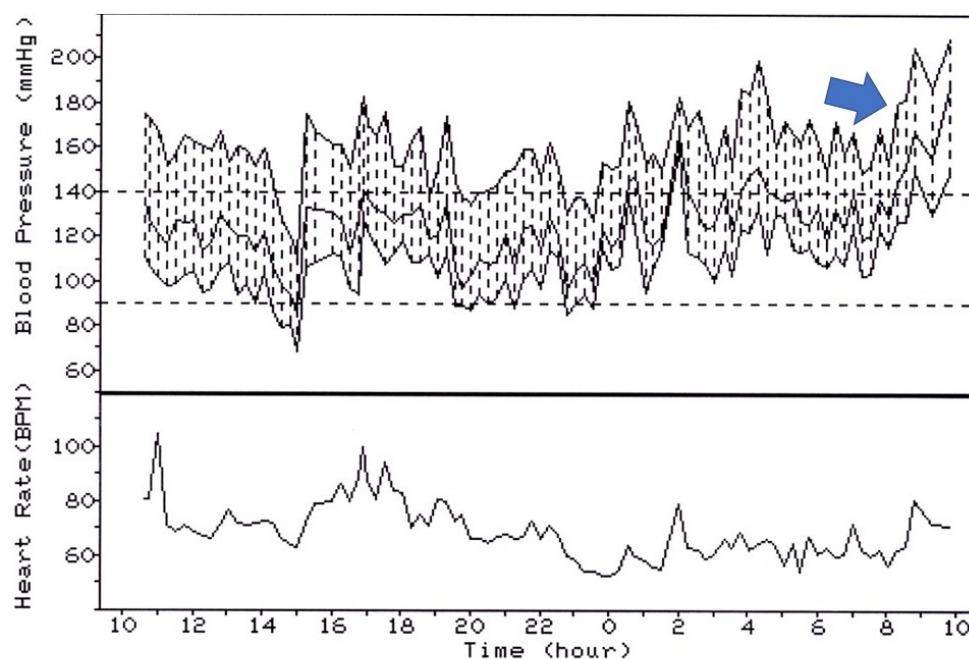


Figure 3. Early morning surge in blood pressure (arrow) in a patient who was not taking antihypertensive drugs during 24 h monitoring. Data from the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study.

Different estimates of the morning surge in BP have been proposed [42,66], including the sleep–trough morning BP surge (difference between the average BP during the 2 h following awakening and the lowest nighttime BP) and the pre-awakening morning BP surge (difference between the average BP during the 2 h after awakening and the average BP during the 2 h before awakening).

The early morning BP surge has been linked with vascular disease [67], LVH [68], brain lesions [42], stroke [42], and a composite pool of cardiovascular events [66]. However,

contrary to expectations, we found in a recent analysis of the PIUMA study [56] that an excessive early morning rise in BP was not an independent predictor of increased cardiovascular risk in hypertension. The same analysis found a link between the day–night dip and the morning BP surge [56]. Similarly, the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study provided evidence that the magnitude of the morning BP rise is not associated with the risk of cardiovascular outcomes [69]. In a clinical study by Pierdomenico et al., a high early morning surge was linked with an increased risk of stroke in dippers, but not in non-dippers, among elderly patients with hypertension [70].

4. Blood Pressure Variability

Ambulatory BP variability is traditionally assessed from the standard deviation (SD) of BP measurements over 24 h (or more appropriately, daytime and nighttime periods evaluated separately). However, other indices of BP variability have been proposed [71], including the ‘weighted’ SD of the 24 h mean value [72], BP variability independent of the mean (VIM) [73], maximum minus minimum BP (MMD) [71,74], and variability ratios [75].

Ambulatory BP variability has been extensively investigated in hypertension as a significant determinant of prognosis [13,26,76,77]. Abnormal ambulatory BP variability has been linked to hypertensive target organ damage [77–80], cardiovascular outcomes [81–84], and all-cause death [84,85]. In this setting, an analysis from our group showed that increased variability in systolic BP during the nighttime (defined by SD > 10.8 mmHg) was an independent predictor of cardiac events in initially untreated hypertensive subjects [86]. In this study, 2649 initially untreated hypertensive subjects were followed for up to 16 years (mean follow-up 6 years) [86]. We used SD of daytime and nighttime BP to estimate variability in BP. The group median of SD identified patients with low or high BP variability (13/10 mmHg for daytime systolic/diastolic BP; 11/9 mmHg for nighttime systolic/diastolic BP). There were 167 new cardiac events and 122 new cerebrovascular events at follow-up [86]. The patients with higher BP variability showed a higher rate of cardiac events when compared with those with lower variability, and comparable results were noted for cerebrovascular events. In a fully adjusted multivariable model, increased systolic BP variability during the night was associated with a 51% higher risk of cardiac events [86].

A recent consensus document of the European Society of Hypertension synthesizes current evidence, clinical implications, and unmet needs in the setting of BP variability [76].

5. Pulse Pressure

Pulse pressure (PP) is a well-recognized marker of arterial stiffness. A fundamental mechanism underlying the rise in PP with aging is the stiffening of large arteries. An increased PP is thus a marker of stiff arterial walls, with several adverse implications of potential prognostic value [87]. We found a direct association between elevated neutrophil count, a marker of systemic inflammation, and 24 h ambulatory PP among postmenopausal women with hypertension. Of note, this association remained significant after adjusting for several confounders, including age, serum glucose, and left ventricular hypertrophy [88]. Other studies found an association between PP and carotid atherosclerosis, left ventricular mass, and white matter lesions.

A link between PP and major cardiovascular events has been reported in several studies, and the link was independent of systolic BP and diastolic BP [89,90]. Ambulatory PP was more potent than office PP for risk stratification in hypertensive subjects [43]. This information emerged from a study conducted in 2010 in initially untreated and uncomplicated subjects with essential hypertension [43]. The rates of total cardiovascular events per 100 patient-years in the three tertiles (≤ 45 mmHg, 46–53 mmHg, and > 53 mmHg) of the distribution of average 24 h PP were 1.19, 1.81, and 4.92 (Figure 4). Rates of fatal events were 0.11, 0.17, and 1.23 ($p < 0.01$) [43]. Similar results have been documented for office PP (Figure 4). However, after allowances for other risk factors, cardiovascular morbidity and

mortality was better predicted by ambulatory PP than by office PP, even after controlling for multiple risk factors [43].

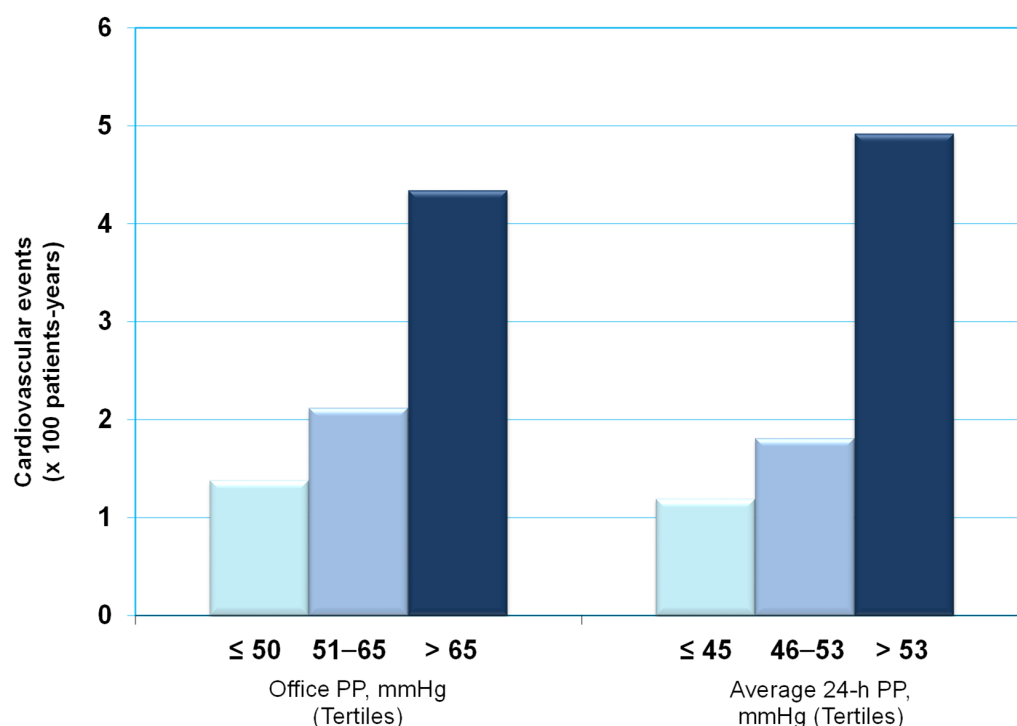


Figure 4. Association between ambulatory/office PP and the risk of cardiovascular events (see text for details). PP = pulse pressure.

In a study conducted in postmenopausal hypertensive women [88], we found that high values for 24 h ambulatory PP are strong predictors of adverse outcomes. Specifically, the rate of cardiovascular events was 1.02, 1.36, and 3.75 per 100 patient-years in the three tertiles (<48 mmHg, 48–56 mmHg, and ≥57 mmHg) of the distribution of 24 h PP ($p < 0.0001$). In a multivariable analysis, 24 h ambulatory PP was an independent predictor of total cardiovascular events. For each 10 mmHg increase in 24 h PP, the risk of total cardiovascular events increased by 73% after controlling for the influence of other risk markers, including age, diabetes, serum creatinine, HDL cholesterol, LDL cholesterol, total white blood cell count, and left ventricular hypertrophy. Notably, office-recorded PP did not achieve significance when used in the same model [88].

Overall, these data strongly suggest that 24 h PP is a strong predictor of major cardiovascular disease events in hypertensive patients.

To further characterize the clinical impact of PP, we also analyzed the different prognostic impact of 24 h mean BP and PP on stroke and coronary artery disease [91]. We analyzed 2311 subjects with essential hypertension prospectively followed for up to 14 years [91]. After allowance for sex, age, and traditional cardiovascular risk factors, for each 10 mmHg increase in 24 h PP, the risk of cardiac events increased by 35% [91]. Unexpectedly, 24 h mean BP was not a significant predictor of cardiac events after controlling for PP [91]. On the other hand, for each 10 mmHg increase in 24 h mean BP, the risk of cerebrovascular events increased by 42%, whereas 24 h PP did not yield significance [91]. Thus, 24 h PP was an independent predictor of cardiac events, and 24 h mean BP was an independent predictor of cerebrovascular events.

These findings strongly suggest that ambulatory mean BP and PP exert a different predictive effect on cardiac and cerebrovascular outcomes [91]. While PP is the dominant predictor of cardiac events, mean BP is the major independent predictor of cerebrovascular events [91].

6. Conclusions

The available evidence supporting the prognostic value of ABPM is remarkable and soundly based on the outcome of prospective clinical studies [92]. ABPM should be considered to optimize the management of hypertensive patients through refinement of cardiovascular risk stratification above and beyond traditional risk markers and office BP. Although another approach to out-of-office BP measurement (i.e., home BP) may be used to provide a better prediction of organ damage and the risk of cardiovascular complications when compared with office BP [93], ABPM should not be replaced by home BP because of its unequivocal superiority under several diagnostic and prognostic aspects [93]. Home BP and ABPM are complementary techniques which should be used with the precise aim of exploiting the best that each technique can provide. ABPM is most appropriate for exploring BP at night and in specific conditions during the day (at work, in smokers, etc.). However, it is more expensive than home BP measurements and cannot be replicated many times. Conversely, self-measured home BP is ideal for long-term monitoring and is advised in almost all patients with hypertension. ABPM should be strongly considered in patients newly diagnosed with hypertension and not yet treated because most of the available outcome-based studies with ABPM have been conducted with this kind of patient. The main limitation of ABPM and home BP is the lack of randomized outcome-based studies comparing a therapeutic regimen based on the above techniques with a regimen based on traditional office BP for the prevention of cardiovascular disease.

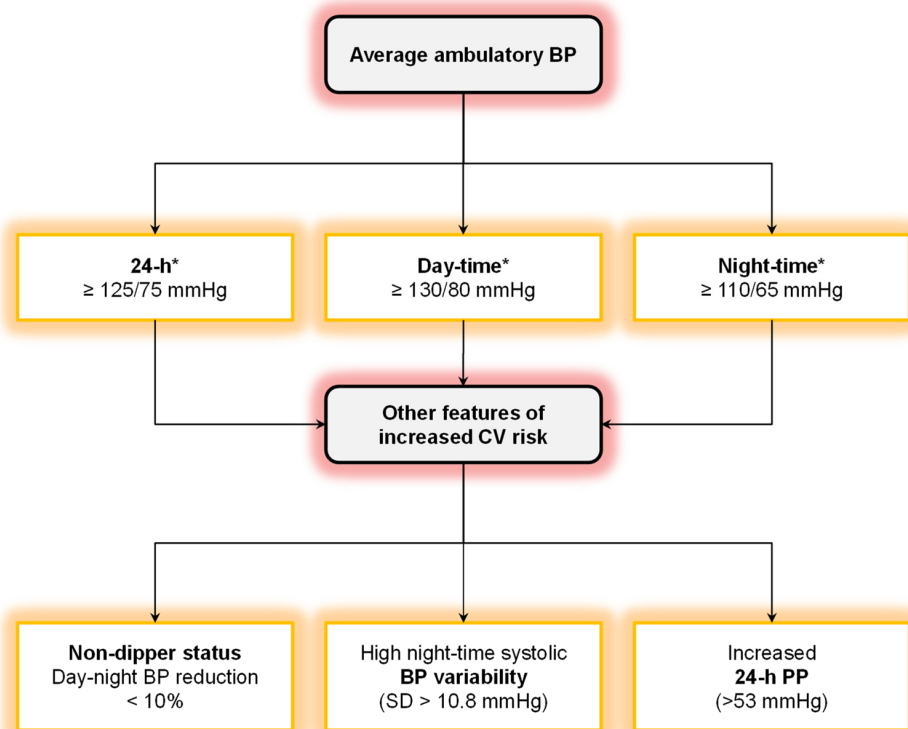
The European Society of Hypertension (ESH) guidelines remark the concept that ABPM and self-measured home BP are valuable alternatives to traditional office BP measurements as it may enable the diagnosis of WCH and MH, which would not be possible using office BP alone. ABPM has advantages over home BP in terms of enabling multiple nighttime BP readings, its possible use in real-life settings (work place, etc.), and more extensive evidence from the literature supporting it [1]. Self-measured home BP has the advantages of allowing BP monitoring for longer periods, although with fewer measurements per unit of time, and being relatively less expensive and more widely available [1].

Average 24 h, daytime, and nighttime BP remain the main components of the ambulatory BP profile proven to be prognostically significant (Figure 5). Other ambulatory measures are being investigated, including sophisticated estimations of BP variability, day–night BP changes, and morning BP surges. Their correct implementation in clinical practice of ABPM needs a standardization of methods.

Several algorithms for the clinical use of ABPM have been proposed. However, in our opinion, the interpretation of ABPM should be simplified in individual patients to optimize their management. We should probably focus on those components of ABPM which more clearly improved risk stratification in long-term outcome studies:

- Average ambulatory BP;
- Pulse pressure;
- Dipping status;
- Variability.

We suggest the use of the mnemonic ‘Ambulatory Does Prediction Valid’ (**A-D-P-V**: Average ambulatory BP; Dipping pattern; Pulse pressure; Variability in ambulatory BP) to correctly refine cardiovascular risk stratification and adapt treatment strategies (Figure 5). In subjects with office BP $\geq 140/90$ mmHg, 24 h ambulatory BP identifies low-risk individuals with normal or optimal values ($<130/80$ mmHg) of daytime ambulatory BP (i.e., white coat hypertension without comorbidities and target organ damage) [6]. Conversely, increased 24 h PP (>53 mmHg), a non-dipping BP pattern (day–night BP reduction $< 10\%$), or increased nighttime systolic BP variability (SD > 10.8 mmHg) in subjects with elevated daytime BP identifies patients at increased cardiovascular risk, regardless of office BP measurements [5].



*Based on ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults

Figure 5. Association between ambulatory/office PP and the risk of cardiovascular events (see text for details). PP = pulse pressure. From ref. [2].

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References

- Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [\[CrossRef\]](#) [\[PubMed\]](#)
- Whelton, P.K.; Carey, R.M.; Aronow, W.S.; Casey, D.E., Jr.; Collins, K.J.; Dennison Himmelfarb, C.; DePalma, S.M.; Gidding, S.; Jamerson, K.A.; Jones, D.W.; et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2018**, *71*, e127–e248. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mancia, G.; Verdecchia, P. Clinical value of ambulatory blood pressure: Evidence and limits. *Circ. Res.* **2015**, *116*, 1034–1045. [\[CrossRef\]](#) [\[PubMed\]](#)
- Boggia, J.; Li, Y.; Thijs, L.; Hansen, T.W.; Kikuya, M.; Bjorklund-Bodegard, K.; Richart, T.; Ohkubo, T.; Kuznetsova, T.; Torp-Pedersen, C.; et al. Prognostic accuracy of day versus night ambulatory blood pressure: A cohort study. *Lancet* **2007**, *370*, 1219–1229. [\[CrossRef\]](#) [\[PubMed\]](#)
- Angeli, F.; Reboldi, G.; Verdecchia, P. Masked hypertension: Evaluation, prognosis, and treatment. *Am. J. Hypertens.* **2010**, *23*, 941–948. [\[CrossRef\]](#)
- Angeli, F.; Verdecchia, P.; Gattobigio, R.; Sardone, M.; Reboldi, G. White-coat hypertension in adults. *Blood Press. Monit.* **2005**, *10*, 301–305. [\[CrossRef\]](#)
- Verdecchia, P.; Angeli, F.; Borgioni, C.; Gattobigio, R.; Reboldi, G. Ambulatory blood pressure and cardiovascular outcome in relation to perceived sleep deprivation. *Hypertension* **2007**, *49*, 777–783. [\[CrossRef\]](#)

8. Verdecchia, P.; Angeli, F.; Borgioni, C.; Repaci, S.; Guerrieri, M.; Andreani, F.; Garofoli, M.; Reboldi, G. Prognostic value of circadian blood pressure changes in relation to differing measures of day and night. *J. Am. Soc. Hypertens.* **2008**, *2*, 88–96. [\[CrossRef\]](#)
9. Verdecchia, P.; Reboldi, G.; Gattobigio, R.; Bentivoglio, M.; Borgioni, C.; Angeli, F.; Carluccio, E.; Sardone, M.G.; Porcellati, C. Atrial fibrillation in hypertension: Predictors and outcome. *Hypertension* **2003**, *41*, 218–223. [\[CrossRef\]](#)
10. Verdecchia, P.; Reboldi, G.P.; Angeli, F.; Schillaci, G.; Schwartz, J.E.; Pickering, T.G.; Imai, Y.; Ohkubo, T.; Kario, K. Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension* **2005**, *45*, 203–208. [\[CrossRef\]](#)
11. Burszty, M.; Ben-Dov, I.Z. Diabetes Mellitus and 24-Hour Ambulatory Blood Pressure Monitoring. *Hypertension* **2009**, *53*, 110–111. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Parati, G.; Bilo, G. Should 24-h Ambulatory Blood Pressure Monitoring Be Done in Every Patient With Diabetes? *Diabetes Care* **2009**, *32*, S298–S304. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Parati, G.; Ochoa, J.E.; Salvi, P.; Lombardi, C.; Bilo, G. Prognostic value of blood pressure variability and average blood pressure levels in patients with hypertension and diabetes. *Diabetes Care* **2013**, *36* (Suppl. 2), S312–S324. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Parati, G.; Stergiou, G.; O'Brien, E.; Asmar, R.; Beilin, L.; Bilo, G.; Clement, D.; de la Sierra, A.; de Leeuw, P.; Dolan, E.; et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J. Hypertens.* **2014**, *32*, 1359–1366. [\[CrossRef\]](#)
15. Ohkubo, T.; Imai, Y.; Tsuji, I.; Nagai, K.; Watanabe, N.; Minami, N.; Itoh, O.; Bando, T.; Sakuma, M.; Fukao, A.; et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: A pilot study in Ohasama. *J. Hypertens.* **1997**, *15*, 357–364. [\[CrossRef\]](#)
16. Bjorklund, K.; Lind, L.; Zethelius, B.; Andren, B.; Lithell, H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation* **2003**, *107*, 1297–1302. [\[CrossRef\]](#)
17. Hansen, T.W.; Kikuya, M.; Thijs, L.; Bjorklund-Bodegard, K.; Kuznetsova, T.; Ohkubo, T.; Richart, T.; Torp-Pedersen, C.; Lind, L.; Jeppesen, J.; et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: A meta-analysis of 7030 individuals. *J. Hypertens.* **2007**, *25*, 1554–1564. [\[CrossRef\]](#)
18. Staessen, J.A.; Thijs, L.; Fagard, R.; O'Brien, E.T.; Clement, D.; de Leeuw, P.W.; Mancia, G.; Nachev, C.; Palatini, P.; Parati, G.; et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* **1999**, *282*, 539–546. [\[CrossRef\]](#)
19. Redon, J.; Campos, C.; Narciso, M.L.; Rodicio, J.L.; Pascual, J.M.; Ruilope, L.M. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: A prospective study. *Hypertension* **1998**, *31*, 712–718. [\[CrossRef\]](#)
20. Verdecchia, P.; Porcellati, C.; Schillaci, G.; Borgioni, C.; Ciucci, A.; Battistelli, M.; Guerrieri, M.; Gatteschi, C.; Zampi, I.; Santucci, A.; et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* **1994**, *24*, 793–801. [\[CrossRef\]](#)
21. Verdecchia, P.; Reboldi, G.; Porcellati, C.; Schillaci, G.; Pede, S.; Bentivoglio, M.; Angeli, F.; Norgiolini, S.; Ambrosio, G. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J. Am. Coll. Cardiol.* **2002**, *39*, 878–885. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Clement, D.L.; De Buyzere, M.L.; De Bacquer, D.A.; de Leeuw, P.W.; Duprez, D.A.; Fagard, R.H.; Gheeraert, P.J.; Missault, L.H.; Braun, J.J.; Six, R.O.; et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N. Engl. J. Med.* **2003**, *348*, 2407–2415. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Dolan, E.; Stanton, A.; Thijs, L.; Hinedi, K.; Atkins, N.; McClory, S.; Den Hond, E.; McCormack, P.; Staessen, J.A.; O'Brien, E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: The Dublin outcome study. *Hypertension* **2005**, *46*, 156–161. [\[CrossRef\]](#)
24. Sega, R.; Facchetti, R.; Bombelli, M.; Cesana, G.; Corrao, G.; Grassi, G.; Mancia, G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: Follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* **2005**, *111*, 1777–1783. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Coccina, F.; Pierdomenico, A.M.; Cuccurullo, C.; Pizzicannella, J.; Guagnano, M.T.; Renda, G.; Trubiani, O.; Cipollone, F.; Pierdomenico, S.D. Prognostic value of non-resistant and resistant masked uncontrolled hypertension detected by ambulatory blood pressure monitoring. *J. Clin. Hypertens.* **2022**, *24*, 591–597. [\[CrossRef\]](#)
26. O'Brien, E.; Parati, G.; Stergiou, G.; Asmar, R.; Beilin, L.; Bilo, G.; Clement, D.; de la Sierra, A.; de Leeuw, P.; Dolan, E.; et al. European society of hypertension position paper on ambulatory blood pressure monitoring. *J. Hypertens.* **2013**, *31*, 1731–1768. [\[CrossRef\]](#)
27. Pickering, T.G.; James, G.D.; Boddie, C.; Harshfield, G.A.; Blank, S.; Laragh, J.H. How common is white coat hypertension? *JAMA* **1988**, *259*, 225–228. [\[CrossRef\]](#)
28. White, W.B.; Wolfson, L.; Wakefield, D.B.; Hall, C.B.; Campbell, P.; Moscufo, N.; Schmidt, J.; Kaplan, R.F.; Pearlson, G.; Guttmann, C.R. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation* **2011**, *124*, 2312–2319. [\[CrossRef\]](#)
29. Mancia, G.; Grassi, G. The Heterogeneous Nature of White-Coat Hypertension. *J. Am. Coll. Cardiol.* **2016**, *68*, 2044–2046. [\[CrossRef\]](#)
30. Mancia, G. White-coat hypertension: Growing evidence in favour of its adverse prognostic significance. *J. Hypertens.* **2017**, *35*, 710–712. [\[CrossRef\]](#)

31. Pierdomenico, S.D.; Lapenna, D.; Bucci, A.; Di Iorio, A.; Neri, M.; Cuccurullo, F.; Mezzetti, A. Cardiovascular and renal events in uncomplicated mild hypertensive patients with sustained and white coat hypertension. *Am. J. Hypertens.* **2004**, *17*, 876–881. [[CrossRef](#)] [[PubMed](#)]
32. Kario, K.; Shimada, K.; Schwartz, J.E.; Matsuo, T.; Hoshide, S.; Pickering, T.G. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J. Cardiol.* **2002**, *39*, 52–54. [[CrossRef](#)] [[PubMed](#)]
33. Pierdomenico, S.D.; Pierdomenico, A.M.; Coccina, F.; Clement, D.L.; De Buyzere, M.L.; De Bacquer, D.A.; Ben-Dov, I.Z.; Vongpatanasin, W.; Banegas, J.R.; Ruilope, L.M.; et al. Prognostic Value of Masked Uncontrolled Hypertension. *Hypertension* **2018**, *72*, 862–869. [[CrossRef](#)] [[PubMed](#)]
34. Pierdomenico, S.D.; Pierdomenico, A.M.; Coccina, F.; Porreca, E. Prognosis of Masked and White Coat Uncontrolled Hypertension Detected by Ambulatory Blood Pressure Monitoring in Elderly Treated Hypertensive Patients. *Am. J. Hypertens.* **2017**, *30*, 1106–1111. [[CrossRef](#)]
35. Pierdomenico, S.D.; Cuccurullo, F.; Mezzetti, A. Masked hypertension in treated hypertensive patients. *Am. J. Hypertens.* **2006**, *19*, 873–874. [[CrossRef](#)]
36. Bobrie, G.; Chatellier, G.; Genes, N.; Clerson, P.; Vaur, L.; Vaisse, B.; Menard, J.; Mallion, J.M. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* **2004**, *291*, 1342–1349. [[CrossRef](#)]
37. Mancia, G. Short- and long-term blood pressure variability: Present and future. *Hypertension* **2012**, *60*, 512–517. [[CrossRef](#)]
38. Zakopoulos, N.A.; Tzoumanidis, S.T.; Barlas, G.J.; Nanas, S.N.; Lekakis, J.P.; Stamatiopoulos, S.F.; Mouloupoulos, S.D. A pressure-time index for assessing the severity of essential hypertension. *J. Hypertens.* **1999**, *17*, 1387–1393. [[CrossRef](#)]
39. Andrade, S.S.; Serro-Azul, J.B.; Nussbacher, A.; Giorgi, D.; Pierri, H.; Gebara, O.; Wajngarten, M. Daytime systolic blood pressure load and previous stroke predict cardiovascular events in treated octogenarians with hypertension. *J. Am. Geriatr. Soc.* **2010**, *58*, 2232–2234. [[CrossRef](#)]
40. Dolan, E.; Li, Y.; Thijs, L.; McCormack, P.; Staessen, J.A.; O'Brien, E.; Stanton, A. Ambulatory arterial stiffness index: Rationale and methodology. *Blood Press. Monit.* **2006**, *11*, 103–105. [[CrossRef](#)]
41. Kario, K.; Matsuo, T.; Kobayashi, H.; Imiya, M.; Matsuo, M.; Shimada, K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* **1996**, *27*, 130–135. [[CrossRef](#)] [[PubMed](#)]
42. Kario, K.; Pickering, T.G.; Umeda, Y.; Hoshide, S.; Hoshide, Y.; Morinari, M.; Murata, M.; Kuroda, T.; Schwartz, J.E.; Shimada, K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. *Circulation* **2003**, *107*, 1401–1406. [[CrossRef](#)] [[PubMed](#)]
43. Verdecchia, P.; Schillaci, G.; Borgioni, C.; Ciucci, A.; Pede, S.; Porcellati, C. Ambulatory pulse pressure: A potent predictor of total cardiovascular risk in hypertension. *Hypertension* **1998**, *32*, 983–988. [[CrossRef](#)] [[PubMed](#)]
44. White, W.B.; Dey, H.M.; Schulman, P. Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild-to-moderate hypertension. *Am. Heart J.* **1989**, *118*, 782–795. [[CrossRef](#)] [[PubMed](#)]
45. Zachariah, P.K.; Sheps, S.G.; Ilstrup, D.M.; Long, C.R.; Bailey, K.R.; Wiltgen, C.M.; Carlson, C.A. Blood pressure load—A better determinant of hypertension. *Mayo Clin. Proc.* **1988**, *63*, 1085–1091. [[CrossRef](#)]
46. Littler, W.A.; West, M.J.; Honour, A.J.; Sleight, P. The variability of arterial pressure. *Am. Heart J.* **1978**, *95*, 180–186. [[CrossRef](#)]
47. Mancia, G.; Ferrari, A.; Gregorini, L.; Parati, G.; Pomidossi, G.; Bertinieri, G.; Grassi, G.; di Rienzo, M.; Pedotti, A.; Zanchetti, A. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ. Res.* **1983**, *53*, 96–104. [[CrossRef](#)]
48. Parati, G.; Pomidossi, G.; Casadei, R.; Malaspina, D.; Colombo, A.; Ravogli, A.; Mancia, G. Ambulatory blood pressure monitoring does not interfere with the haemodynamic effects of sleep. *J. Hypertens. Suppl. Off. J. Int. Soc. Hypertens.* **1985**, *3*, S107–S109.
49. O'Brien, E.; Sheridan, J.; O'Malley, K. Dippers and non-dippers. *Lancet* **1988**, *2*, 397. [[CrossRef](#)]
50. Pickering, T.G. How should the diurnal changes of blood pressure be expressed? *Am. J. Hypertens.* **1995**, *8*, 681–682. [[CrossRef](#)]
51. Kario, K.; Shimada, K. Risers and extreme-dippers of nocturnal blood pressure in hypertension: Antihypertensive strategy for nocturnal blood pressure. *Clin. Exp. Hypertens.* **2004**, *26*, 177–189. [[CrossRef](#)] [[PubMed](#)]
52. Bellelli, G.; Frisoni, G.B.; Lucchi, E.; Guerini, F.; Geroldi, C.; Magnifico, F.; Bianchetti, A.; Trabucchi, M. Blunted reduction in night-time blood pressure is associated with cognitive deterioration in subjects with long-standing hypertension. *Blood Press. Monit.* **2004**, *9*, 71–76. [[CrossRef](#)] [[PubMed](#)]
53. Bianchi, S.; Bigazzi, R.; Baldari, G.; Sgherri, G.; Campese, V.M. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am. J. Hypertens.* **1994**, *7*, 23–29. [[CrossRef](#)] [[PubMed](#)]
54. Mousa, T.; el-Sayed, M.A.; Motawea, A.K.; Salama, M.A.; Elhendy, A. Association of blunted nighttime blood pressure dipping with coronary artery stenosis in men. *Am. J. Hypertens.* **2004**, *17*, 977–980. [[CrossRef](#)] [[PubMed](#)]
55. Fagard, R.H.; Staessen, J.A.; Thijs, L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* **1997**, *29*, 22–29. [[CrossRef](#)] [[PubMed](#)]
56. Verdecchia, P.; Angeli, F.; Mazzotta, G.; Garofoli, M.; Ramundo, E.; Gentile, G.; Ambrosio, G.; Reboldi, G. Day-night dip and early-morning surge in blood pressure in hypertension: Prognostic implications. *Hypertension* **2012**, *60*, 34–42. [[CrossRef](#)] [[PubMed](#)]

57. Palatini, P.; Reboldi, G.; Saladini, F.; Angeli, F.; Mos, L.; Rattazzi, M.; Vriz, O.; Verdecchia, P. Dipping pattern and short-term blood pressure variability are stronger predictors of cardiovascular events than average 24-h blood pressure in young hypertensive subjects. *Eur. J. Prev. Cardiol.* **2022**, *29*, 1377–1386. [\[CrossRef\]](#)
58. Verdecchia, P.; Angeli, F.; Reboldi, G. Chronic Kidney Disease and Left Ventricular Hypertrophy. Potent Modifiers of the Prognostic Impact of Circadian Blood Pressure Changes. *Hypertension* **2022**, *79*, 1028–1036. [\[CrossRef\]](#)
59. Verdecchia, P.; Angeli, F.; Sardone, M.; Borgioni, C.; Garofoli, M.; Reboldi, G. Is the definition of daytime and nighttime blood pressure prognostically relevant? *Blood Press. Monit.* **2008**, *13*, 153–155. [\[CrossRef\]](#)
60. Yamamoto, Y.; Akiguchi, I.; Oiwa, K.; Hayashi, M.; Kimura, J. Adverse effect of nighttime blood pressure on the outcome of lacunar infarct patients. *Stroke* **1998**, *29*, 570–576. [\[CrossRef\]](#)
61. Ohkubo, T.; Imai, Y.; Tsuji, I.; Nagai, K.; Watanabe, N.; Minami, N.; Kato, J.; Kikuchi, N.; Nishiyama, A.; Aihara, A.; et al. Relation between nocturnal decline in blood pressure and mortality. The Ohasama Study. *Am. J. Hypertens.* **1997**, *10*, 1201–1207. [\[CrossRef\]](#) [\[PubMed\]](#)
62. White, W.B. Clinical assessment of early morning blood pressure in patients with hypertension. *Prev. Cardiol.* **2007**, *10*, 210–214. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Hoshida, S.; Kario, K. Early morning hypertension: A narrative review. *Blood Press. Monit.* **2013**, *18*, 291–296. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Hoshida, S.; Kario, K. Early morning hypertension/morning blood pressure surge. *Nihon Rinsho* **2014**, *72*, 1395–1399. [\[PubMed\]](#)
65. Kario, K.; White, W.B. Early morning hypertension: What does it contribute to overall cardiovascular risk assessment? *J. Am. Soc. Hypertens.* **2008**, *2*, 397–402. [\[CrossRef\]](#)
66. Li, Y.; Thijs, L.; Hansen, T.W.; Kikuya, M.; Boggia, J.; Richart, T.; Metoki, H.; Ohkubo, T.; Torp-Pedersen, C.; Kuznetsova, T.; et al. Prognostic value of the morning blood pressure surge in 5645 subjects from 8 populations. *Hypertension* **2010**, *55*, 1040–1048. [\[CrossRef\]](#)
67. Marfella, R.; Siniscalchi, M.; Nappo, F.; Gualdiero, P.; Esposito, K.; Sasso, F.C.; Cacciapuoti, F.; Di Filippo, C.; Rossi, F.; D'Amico, M.; et al. Regression of carotid atherosclerosis by control of morning blood pressure peak in newly diagnosed hypertensive patients. *Am. J. Hypertens.* **2005**, *18*, 308–318. [\[CrossRef\]](#)
68. Gosse, P.; Ansoborlo, P.; Lemetayer, P.; Clementy, J. Left ventricular mass is better correlated with arising blood pressure than with office or occasional blood pressure. *Am. J. Hypertens.* **1997**, *10*, 505–510. [\[CrossRef\]](#)
69. Bombelli, M.; Fodri, D.; Toso, E.; Macchiarulo, M.; Cairo, M.; Facchetti, R.; Dell'Oro, R.; Grassi, G.; Mancia, G. Relationship among morning blood pressure surge, 24-hour blood pressure variability, and cardiovascular outcomes in a white population. *Hypertension* **2014**, *64*, 943–950. [\[CrossRef\]](#)
70. Pierdomenico, S.D.; Pierdomenico, A.M.; Cuccurullo, F. Morning blood pressure surge, dipping, and risk of ischemic stroke in elderly patients treated for hypertension. *Am. J. Hypertens.* **2014**, *27*, 564–570. [\[CrossRef\]](#)
71. Asayama, K.; Schutte, R.; Li, Y.; Hansen, T.W.; Staessen, J.A. Blood pressure variability in risk stratification: What does it add? *Clin. Exp. Pharmacol. Physiol.* **2014**, *41*, 1–8. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Bilo, G.; Giglio, A.; Styczkiewicz, K.; Caldara, G.; Maronati, A.; Kawecka-Jaszcz, K.; Mancia, G.; Parati, G. A new method for assessing 24-h blood pressure variability after excluding the contribution of nocturnal blood pressure fall. *J. Hypertens.* **2007**, *25*, 2058–2066. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Rothwell, P.M.; Howard, S.C.; Dolan, E.; O'Brien, E.; Dobson, J.E.; Dahlof, B.; Sever, P.S.; Poulter, N.R. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* **2010**, *375*, 895–905. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Masugata, H.; Senda, S.; Murao, K.; Inukai, M.; Hosomi, N.; Iwado, Y.; Noma, T.; Kohno, M.; Himoto, T.; Goda, F. Visit-to-visit variability in blood pressure over a 1-year period is a marker of left ventricular diastolic dysfunction in treated hypertensive patients. *Hypertens. Res.* **2011**, *34*, 846–850. [\[CrossRef\]](#)
75. Gavish, B.; Burszty, M. Blood pressure and heart period variability ratios derived from 24-hour ambulatory measurements are predictors of all-cause mortality. *J. Hypertens.* **2015**, *33*, 491–498. [\[CrossRef\]](#)
76. Parati, G.; Bilo, G.; Kollias, A.; Pengo, M.; Ochoa, J.E.; Castiglioni, P.; Stergiou, G.S.; Mancia, G.; Asayama, K.; Asmar, R.; et al. Blood pressure variability: Methodological aspects, clinical relevance and practical indications for management—A European Society of Hypertension position paper *. *J. Hypertens.* **2023**, *41*, 527–544. [\[CrossRef\]](#)
77. Parati, G.; Pomidossi, G.; Albini, F.; Malaspina, D.; Mancia, G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J. Hypertens.* **1987**, *5*, 93–98. [\[CrossRef\]](#)
78. Tatasciore, A.; Renda, G.; Zimarino, M.; Soccio, M.; Bilo, G.; Parati, G.; Schillaci, G.; De Caterina, R. Awake systolic blood pressure variability correlates with target-organ damage in hypertensive subjects. *Hypertension* **2007**, *50*, 325–332. [\[CrossRef\]](#)
79. Kawai, T.; Ohishi, M.; Kamide, K.; Onishi, M.; Takeya, Y.; Tatara, Y.; Oguro, R.; Yamamoto, K.; Sugimoto, K.; Rakugi, H. The impact of visit-to-visit variability in blood pressure on renal function. *Hypertens. Res.* **2012**, *35*, 239–243. [\[CrossRef\]](#)
80. Matsui, Y.; Ishikawa, J.; Eguchi, K.; Shibasaki, S.; Shimada, K.; Kario, K. Maximum value of home blood pressure: A novel indicator of target organ damage in hypertension. *Hypertension* **2011**, *57*, 1087–1093. [\[CrossRef\]](#)
81. Johansson, J.K.; Niiranen, T.J.; Puukka, P.J.; Julia, A.M. Prognostic value of the variability in home-measured blood pressure and heart rate: The Finn-Home Study. *Hypertension* **2012**, *59*, 212–218. [\[CrossRef\]](#) [\[PubMed\]](#)

82. Kikuya, M.; Hozawa, A.; Ohokubo, T.; Tsuji, I.; Michimata, M.; Matsubara, M.; Ota, M.; Nagai, K.; Araki, T.; Satoh, H.; et al. Prognostic significance of blood pressure and heart rate variabilities: The Ohasama study. *Hypertension* **2000**, *36*, 901–906. [[CrossRef](#)] [[PubMed](#)]
83. Shimbo, D.; Newman, J.D.; Aragaki, A.K.; LaMonte, M.J.; Bavry, A.A.; Allison, M.; Manson, J.E.; Wassertheil-Smoller, S. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: Data from the Women's Health Initiative. *Hypertension* **2012**, *60*, 625–630. [[CrossRef](#)] [[PubMed](#)]
84. Palatini, P.; Reboli, G.; Beilin, L.J.; Casiglia, E.; Eguchi, K.; Imai, Y.; Kario, K.; Ohkubo, T.; Pierdomenico, S.D.; Schwartz, J.E.; et al. Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: The Ambulatory Blood Pressure-International Study. *Hypertension* **2014**, *64*, 487–493. [[CrossRef](#)] [[PubMed](#)]
85. Muntner, P.; Shimbo, D.; Tonelli, M.; Reynolds, K.; Arnett, D.K.; Oparil, S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: Findings from NHANES III, 1988 to 1994. *Hypertension* **2011**, *57*, 160–166. [[CrossRef](#)]
86. Verdecchia, P.; Angeli, F.; Gattobigio, R.; Rapisetta, C.; Reboli, G. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am. J. Hypertens.* **2007**, *20*, 154–161. [[CrossRef](#)] [[PubMed](#)]
87. Coccina, F.; Pierdomenico, A.M.; Cuccurullo, C.; Pizzicannella, J.; Trubiani, O.; Pierdomenico, S.D. Prognostic Impact of 24-Hour Pulse Pressure Components in Treated Hypertensive Patients Older Than 65 Years. *Diagnostics* **2023**, *13*, 845. [[CrossRef](#)]
88. Angeli, F.; Angeli, E.; Ambrosio, G.; Mazzotta, G.; Cavallini, C.; Reboli, G.; Verdecchia, P. Neutrophil count and ambulatory pulse pressure as predictors of cardiovascular adverse events in postmenopausal women with hypertension. *Am. J. Hypertens.* **2011**, *24*, 591–598. [[CrossRef](#)]
89. Madhavan, S.; Ooi, W.L.; Cohen, H.; Alderman, M.H. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* **1994**, *23*, 395–401. [[CrossRef](#)]
90. Safar, M. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* **1994**, *24*, 368. [[CrossRef](#)]
91. Verdecchia, P.; Schillaci, G.; Reboli, G.; Franklin, S.S.; Porcellati, C. Different prognostic impact of 24-hour mean blood pressure and pulse pressure on stroke and coronary artery disease in essential hypertension. *Circulation* **2001**, *103*, 2579–2584. [[CrossRef](#)] [[PubMed](#)]
92. Piper, M.A.; Evans, C.V.; Burda, B.U.; Margolis, K.L.; O'Connor, E.; Whitlock, E.P. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: A systematic review for the u.s. Preventive services task force. *Ann. Intern. Med.* **2015**, *162*, 192–204. [[CrossRef](#)] [[PubMed](#)]
93. Kantarci, G. Home and ambulatory blood pressure monitoring: When? who? *Kidney Int. Suppl.* **2013**, *3*, 337–339. [[CrossRef](#)] [[PubMed](#)]

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