# I Brazilian Position Paper on Prehypertension, White Coat Hypertension and Masked Hypertension: Diagnosis and Management

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## Introduction

Arterial blood pressure (BP) is a very useful variable in clinical practice. Its measurement is simple, inexpensive and easy; it is worth noting that BP should be accurately obtained, following the recommendations of the VI Brazilian Guidelines on Hypertension (DBH VI)[1].

Office BP measurement is the central parameter for the diagnosis, treatment and follow-up of systemic arterial hypertension (SAH), being directly, continuously and independently related to the risk of fatal and non-fatal cardiovascular (CV) events[1-3].

Thus, the consideration of BP values closer to the upper limits of normality, the so-called prehypertension (PH)[2], and intervention on those values have been emphasized over the last decade, because PH represents an important opportunity to prevent established SAH, contributing to reduce the associated CV risk.

Repeated BP measurement at the office allows the diagnosis of hypertension and normotension. To better assess BP behavior, there are methods that analyze BP by using a higher number of measurements, minimizing interferences of the environment, situation and observer. Those alternatives are as follows: 24-hour ambulatory BP monitoring (ABPM); and dwelling BP measurement [home BP monitoring (HBPM) and BP self-measurement (BPSM)]. Based on those methods, two other BP classifications were adopted: white coat hypertension (WCH) and masked hypertension (MH)[1,3-5] (Figure 1).

Epidemiological and clinical studies on those conditions are still limited; however, they deserve attention because of their higher CV risk as compared with normotension[6,7].

This document represents the position of the Brazilian Society of Cardiology Arterial Hypertension Department (DHA/SBC) on the diagnosis and non-drug and drug therapy for PH, WCH and MH, aiming at contributing to a better clinical practice.

## Prehypertension

### Epidemiology

The term PH was described in 2003 on the American Guideline on Arterial Hypertension[1] that emphasized the importance of adopting strict preventive measures in the presence of PH, considering that individuals with such characteristics have a higher incidence of SAH in the following years and greater CV risk than those with optimal BP (lower than 120/80 mm Hg)[2,3]. A study has shown that among prehypertensive individuals aged 40-49 years, the incidence of hypertension in the following years is 80%[8].

In the PURE (Prospective Urban and Rural Epidemiological) Study, assessing 153,996 individuals in 17 countries, PH prevalence was 36.8%, greater than the SAH rate (34.3%). Data on the North American adult population have shown a 40% prevalence[9].

Prehypertension is known to be often associated with other CV risk factors, such as obesity, insulin resistance, diabetes mellitus, dyslipidemia and other metabolic syndrome phenotypes, resulting in early vascular abnormalities and progression to atherosclerosis[10].

### Diagnosis and clinical strategies of identification

Prehypertension has been defined as office measurements of systolic blood pressure (SBP) between 120 and 139 mm Hg and/or of diastolic blood pressure (DBP) between 80 and 89 mmHg[2]. Its identification depends on regular BP measurement, which is recommended to be performed at least once a year.

The diagnosis of PH is based on BP measurement at the office, but that diagnosis can certainly be improved with 24-hour ABPM and/or HBPM. Such forms of out-of-office BP assessment have the advantage of providing a much higher number of measurements, outside sites where BP is usually taken, representing a more reliable BP registry[4,5]. It is important to identify the presence of MH among prehypertensive individuals.

There is evidence that the increase in left ventricular mass (LVM) in prehypertensive individuals is a strong predictor of the development of SAH within four years, regardless of other metabolic and anthropometric factors associated. The increase in LVM might be associated with a higher daily hemodynamic load that could be detected by measuring BP at the office. Increased BP variability, lack of its drop during sleep or sustained and prolonged increased BP during wakefulness could explain higher LVM values in prehypertensive individuals. In addition, PH progression to hypertension has been associated with increased arterial stiffness[11,12].

### Prognostic value

Prehypertension is a precursor of SAH, associates with other CV risk factors, and has greater CV morbidity and mortality[6,13].

## Keywords

Hypertension / therapy; Prehypertension / prevention & control; White Coat Hypertension; Masked Hypertension.

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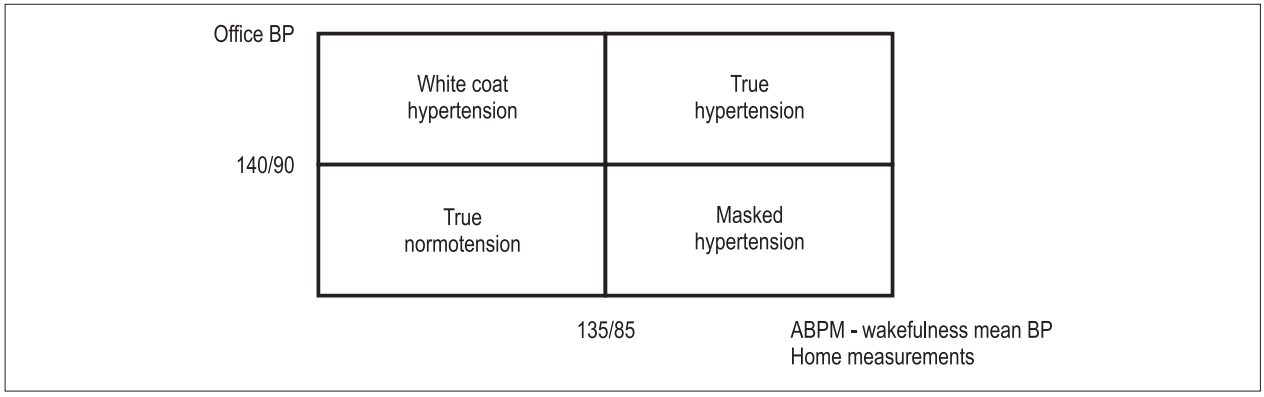


**Figure 1 –** *Classification of blood pressure behavior considering office BP, ABPM and home BP measurements[1]. ABPM: ambulatory blood pressure monitoring; BP: blood pressure.*

In the population assessed in the Framingham study, the following percentages of individuals younger than 65 years developed SAH within a four-year follow-up in the three BP strata considered normal: 5.3% of the individuals with optimal BP; 17.6% of those with normal BP; and 37.3% of those considered to have high-normal BP at the time. For individuals older than 65 years, those rates were 16%, 25.5% and 49.5%, respectively[14]. Data obtained from two British Health and Lifestyle Surveys conducted seven years apart have been used to form a subsample of 2,048 normotensive individuals, and have demonstrated a greater risk for developing SAH among those with higher BP levels, especially the younger ones[15]. Other studies have reported that individuals older than 45 years have a 56.4% progression rate to arterial hypertension in three years (56.9% for men and 55.9% for women)[16].

A population-based study conducted in Brazil has reported that four out of five prehypertensive individuals aged 40-49 years developed SAH in ten years[8].

Regarding the increased risk for CV events of patients with PH, data from longitudinal studies from the Framingham Heart Study have indicated that SBP levels between 130-139 mm Hg and DBP between 85-89 mm Hg are associated with a two-fold increase in the risk for CV diseases (CVD) as compared with 120/80 mmHg levels[14]. That association proved to be more significant in diabetic individuals and those with higher body mass index (BMI)[17]. Individuals with PH are more prone to acute myocardial infarction (AMI) or coronary artery disease (CAD) than those considered normotensive[18]. A Japanese study has reported a 45% increase in the risk of CV events in prehypertensive individuals as compared with normotensive ones, after adjusting for all other traditional risk factors[19].

## White coat hypertension

### Epidemiology

The prevalence of WCH varies because of the diversity of the diagnostic criteria involving not only aspects related to BP measurement but also to the populations studied. The mean overall prevalence of WCH, based on four population-based studies, was 13%, and reached 32% among hypertensives in those studies[20]. In the general population, those values range from 10% to 20%, being more common among children and the elderly, in the female sex, and in non-smokers[21,22].

The prevalence of WCH is also related to office BP measurements, its percentage being 55% among stage 1 hypertensives, and only 10% among stage 3 hypertensives[21]. However, among individuals whose DBP at the office exceeds 105 mm Hg, WCH is an unlikely finding[23]. That phenomenon also occurs among hypertensives undergoing treatment, being called the white coat effect. Muxfeldt et al[24] have assessed uncontrolled hypertensive patients on antihypertensive treatment, of whom more than 60% were on three or more drugs and 37% had the white coat effect. In the PAMELA (*Pressione Arteriose Monitorate E Loro Associazioni*) study, ongoing for ten years, 42.6% of the patients with metabolic syndrome and WCH at the first consultation developed sustained arterial hypertension[25].

The greater the BMI, the higher the WCH prevalence. Helvaci et al[26], studying the BP behavior of individuals assessed at check-up clinics, have reported the following WCH prevalences: 19.6% for individuals with IMC lower than 18.5 kg/m$^2$; 35.6% for individuals with IMC between 18.5 and 24.9 kg/m$^2$; and 68.4% for overweight individuals (IMC between 25 and 29.9 kg/m$^2$)[26].

The WCH frequency increases with age, and, among individuals older than 65 years, its prevalence usually ranges from 43% to 45%[27].

In a follow-up period of up to 6.5 years, Verdecchia et al[28] have reported a 37% risk of developing arterial hypertension in individuals with WCH. That percentage related to baseline values of ABPM rather than to office BP.

### Diagnosis and clinical strategies of identification

The diagnosis of WCH requires office and out-of-office BP measurement, be it by use of ABPM or home measurements[4]. The thresholds recommended are those adopted at the most recent NICE[29] and 2013 ESH/ESC[3] guidelines, and ESH

Position Paper on Ambulatory Blood Pressure Monitoring[5], which maintain the values of the JNC 7[2] and 2003 and 2007 ESH/ESC[30,31] guidelines, and were based on studies such as the IDACO (International Database on Ambulatory Blood Pressure monitoring in relation to Cardiovascular Outcomes Investigators)[32] and Ohasama Study[33] (table 1).

White coat hypertension is characterized as follows: 1) increased office BP levels (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg); and 2) normal out-of-office BP levels (< 135/85 mmHg) measured on ABPM during wakefulness, or at home (HBPM or BPSM), as shown in table 1 and figures 1 and 2. The European Society of Hypertension recommends that, on ABPM, the diagnosis of WCH requires normal mean values of 24-hour BP and of nocturnal BP[5].

Under such conditions, the diagnosis of office arterial hypertension changes to WCH. Individuals with stage 1-2 office hypertension, with neither co-morbidities nor target-organ lesions, should undergo complementary assessment by BP measurement outside the office (figure 3).

The white coat effect is defined as an increase in SBP and DBP ≥ 20 mm Hg and 10 mm Hg, respectively[34], between office BP measurement and the mean BP on ABPM during wakefulness or home measurements, with no change in the diagnosis of normotension or hypertension.

The use of the term 'home measurements' should increase, replacing the terms HBPM and BPSM. Thus, BPSM should be encouraged with validated equipment, cuffs applied to arm, and periodically tested calibration. It differs mainly from HBPM because of the use of a determined protocol, characterizing that both methods have more similarities than differences and can be used together[35].

**Table 1 – Threshold of abnormality to diagnose hypertension on 24-hour ABPM and home BP measurement**

| Out-of-office measurement | SBP and/or DBP (mmHg) |
|---|---|
| **ABPM** | |
| 24-h mean | ≥ 130/80 |
| Wakefulness mean | ≥ 135/85 |
| Sleep mean | ≥ 120/70 |
| Home measurement | ≥ 135/85 |

*ABPM: ambulatory blood pressure monitoring; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

### Prognostic value

Cardiovascular outcomes related to WCH are still controversial. Studies have suggested that WCH has lower risk, similar to that of normotensive individuals, and that risk tends to increase over time. Meta-analysis carried out with

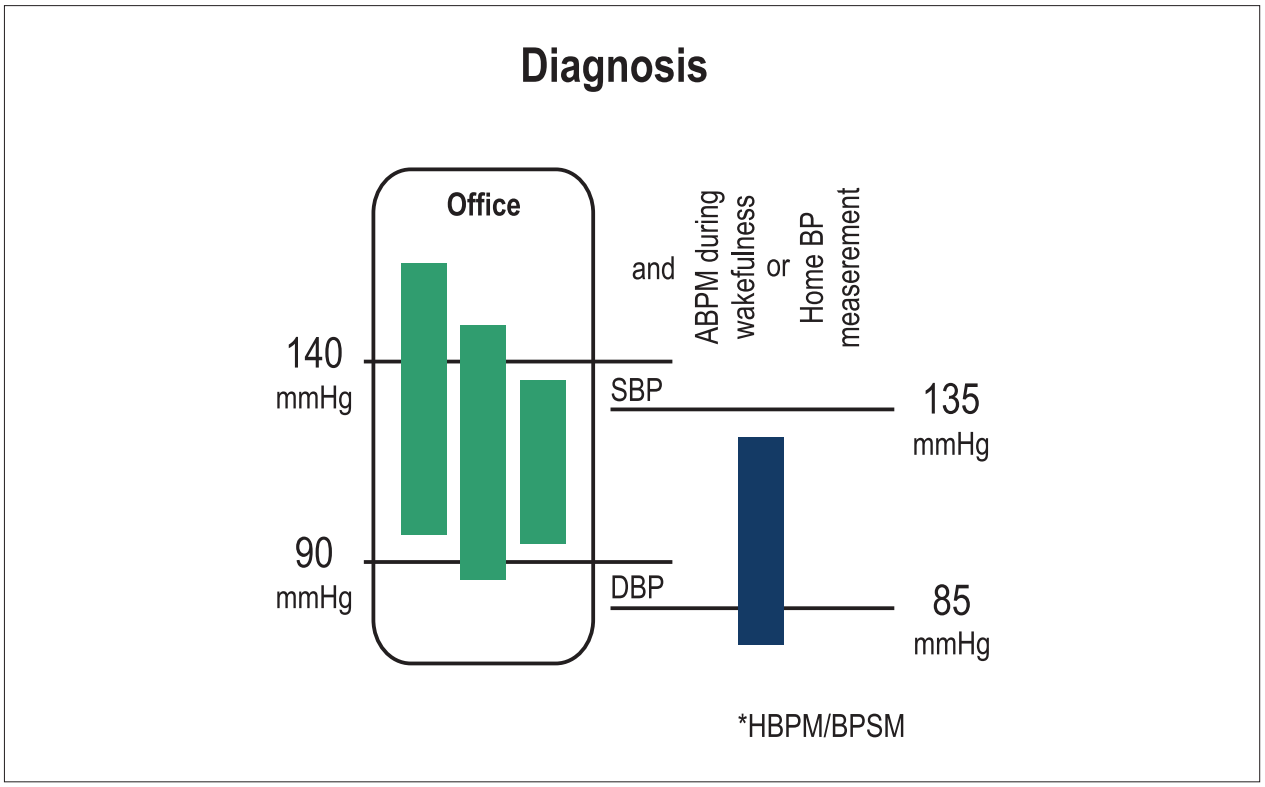


**Figure 2 –** *Schematic representation of BP behavior at the office and on ABPM or home BP measurement for the diagnosis of white coat hypertension. ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; BPSM: blood pressure self-measurement; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

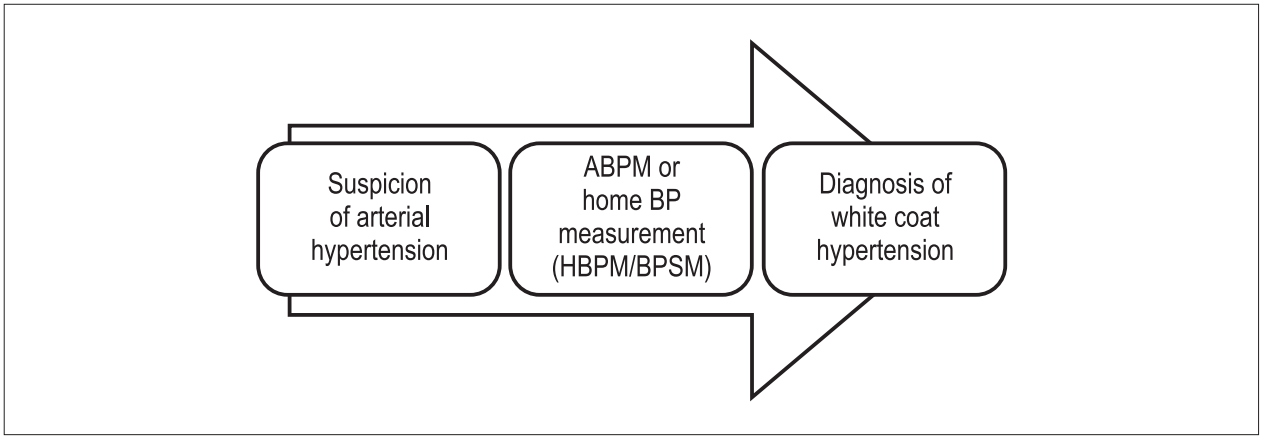


**Figure 3 –** *Flowchart for the identification of white coat hypertension. ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; BPSM: blood pressure self-measurement.*

7,030 individuals has evidenced the existence of increasing CV risk from normotension, to WCH, to MH, and finally, to hypertension[20,36-39].

Regarding the risk of developing hypertension, the PAMELA study has shown that a significantly higher proportion of individuals previously diagnosed with WCH or MH, after ten years were diagnosed with sustained hypertension as compared with previously normotensive individuals[25].

## Masked hypertension

### Epidemiology

Masked hypertension is characterized by normal BP values at the office and abnormal out-of-office BP values, on either ambulatory or dwelling BP measurements (ABPM, HBPM or BPSM)[40].

The prevalence of MH is estimated to range from 8% to 20% among adults with no treatment, and to be at least 50% among individuals on drug treatment[41]. A meta-analysis involving 28 studies has estimated a 16.8% MH prevalence in the general population. Among children, the estimated MH prevalence is 7%[42]. Higher MH prevalence has been observed when office BP is in the high-normal range[41]. Office BP within the normal range as compared to abnormal ambulatory values has been attributed, among other factors, to the "regression toward the mean" phenomenon[40]. Other factors have also correlated with MH[30,40,43-48], as shown in Chart 1. In a study involving 3,400 treated hypertensives, the major factors associated with MH were overweight (1.38; 95% CI: 1.09-1.75) and regular alcohol consumption (OR, 1.37; 95% CI: 1.09-1.72)[42]. In another study, the risk for MH was higher among men than among women [relative risk (RR), 1.14; 95% CI: 1.01-1.28] and among smokers (RR, 1.16; 95% CI: 1.04-1.30)[49]. Another study has shown that women were less prone than men to have MH (OR, 0.39; 95% CI: 0.22- 0.68)[47].

Classically, the presence of MH occurs among untreated individuals. Recently, the literature has emphasized the occurrence of normal office BP and elevated out-of-office BP values in treated individuals. Lower levels of anxiety and the use of antihypertensive drugs only before the medical consultation, with a drug action peak at the time of medical examination, has also been listed as causing factors[44,46,50].

### Diagnosis and clinical strategies of identification

Masked hypertension refers to untreated patients with systematically normal office BP measurements (BP < 140/90 mm Hg) and elevated BP on ABPM or at home measurements - mean BP during wakefulness or mean home BP ≥ 135/85 mm Hg[51,52] (table 1 and figures 1 and 4). It is worth noting the position of the European Society of Hypertension for ABPM, which has also considered the elevated means of 24-hour and nocturnal BP measurements as criteria for MH diagnosis, even with normal mean BP during wakefulness[5].

The conditions listed on Chart 1 are related to MH, and, when present, the diagnosis of MH can be suspected, and ABPM should be considered for a more adequate analysis of the actual BP behavior. The presence of target-organ lesions and the report of repeated high out-of-office BP measurements should raise suspicion of MH[1,3-5,48,53,54].

Masked hypertension can also be identified based on repeated BP measurements in the morning and afternoon with proper sensitivity and specificity[7]. However, several authors have questioned the reproducibility in the long run of the measurements obtained in that way[55].

### Prognostic value

The prognostic value of MH is controversial; while some studies have confirmed its greater CV risk, others have failed to show such relationship. Several authors have reported that ABPM and home BP measurements of hypertensives are better independent predictors of both target-organ lesions[56,57] and CV risk[58] than office BP measurement. However, Cuspidi et al[59], analyzing 13 studies in an attempt to relate MH and left ventricular hypertrophy (LVH), have concluded that the relationship between MH and the development of LVH was limited[59].

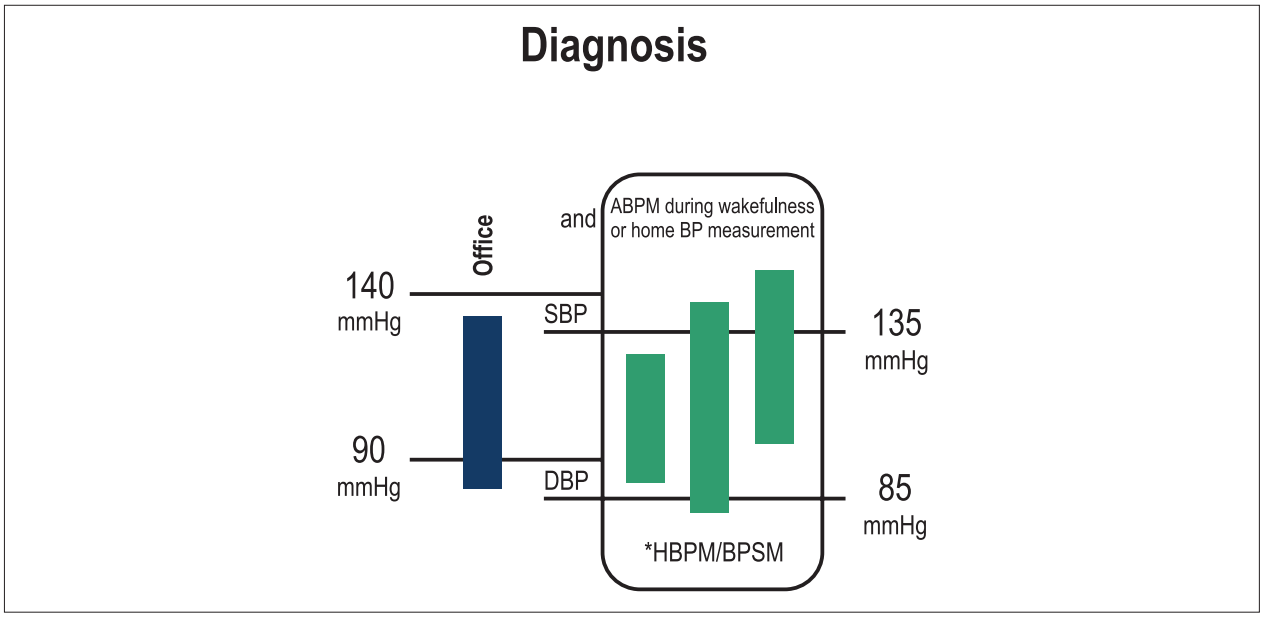


**Figure 4 –** *Schematic representation of BP behavior at the office and on ABPM or home BP measurement for the diagnosis of masked hypertension. ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; BPSM: blood pressure self-measurement; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

**Chart 1 – Factors related to the presence of masked hypertension[2,4-11]**

| |
|---|
| Male sex |
| Young age |
| Family history of arterial hypertension |
| Smoking habit |
| Alcohol consumption |
| Increased physical activity |
| Exertion-induced hypertension |
| Occasionally increased BP measurements |
| Obesity |
| Diabetes |
| Chronic kidney disease |
| Left ventricular hypertrophy |
| Multiple risk factors |
| Sleep apnea |
| Psychosocial factors: anxiety, interpersonal conflicts, stress at workplace |

On the other hand, concentric remodeling and LVH, thickening of the intima-media layer, carotid atherosclerotic plaques and microalbuminuria were more prevalent in MH than in the normotensive population[56].

Hanninen et al[60], assessing the prognostic value of MH in a general population sample in Finland, have included 2,046 normotensive and hypertensive individuals with different CV risk factors. Those authors have reported that, assessing the CV risk by measuring home BP, patients with MH have a higher CV risk adjusted for age as compared with that of normotensive individuals. However, MH was not an independent predictor of CV risk when the baseline home BP measurement was adjusted for other traditional risk factors. They have concluded that home BP values associated with other traditional risk factors are sufficient for CV risk stratification.

Meta-analyses of prospective studies have indicated a two-fold increase in the risk for CV events in MH as compared with true normotension, an incidence similar to that observed in true SAH. The non-detection of MH and the consequent lack of treatment might have contributed to that result[20,37,41].

## Non-drug treatment for prehypertension, white coat hypertension and masked hypertension: efficacy and difficulties for implementation

There is no doubt about the benefits obtained with changes in lifestyle (CLS) for individuals with SAH and prehypertension, and there are good indications that they extend to those with WCH, as well as to those with MH[1,3].

The major CLS aimed at that purpose are as follows: weight control; change to the DASH diet (rich in fruits, vegetables, fibers, minerals and low-fat dairy products); reduced salt intake; reduced alcohol consumption; smoking cessation; physical exercise practice; and psychosocial stress control[1,3].

Several clinical studies assessing those measures have shown a significant BP reduction in hypertensive and prehypertensive individuals, and a delay in the appearance of SAH in the latter[61-68].

Regarding WCH, the encouragement of CLS is based on the following reasons: WCH is not harmless, because individuals with WCH can have changes in target organs; CLS should be the initial strategy to reduce BP in any type of BP behavior change; CLS are recommended as an important strategy to prevent or delay the appearance of SAH in the general population; patients with WCH are more likely to develop sustained SAH; CLS have clear benefits to other CV risk factors; the drug treatment of WCH is still controversial[1,3,20].

In masked hypertension, the recommendations can be more specific according to the period of the day in which BP increases, such as morning, daytime and nocturnal hypertension[69].

The reduction in alcohol consumption and in physical and mental stress is recommended for patients with morning hypertension[70]. Regarding hypertension during wakefulness, smoking cessation is necessary, as well as physical and mental stress control[71]. Those with hypertension during sleep should undergo salt restriction, because that type of hypertension is more often observed in salt-sensitive individuals[72], as well as weight reduction, especially the obese individuals with obstructive sleep apnea syndrome[73].

In addition to close follow-up by a medical professional, the multiprofessional team plays a fundamental role, motivating adherence to treatment and assuring that changes are permanent[1,3,74-76].

Despite evidence, the great limitation and reason of distrust is the effectiveness of those CLS measures out of the context of clinical trials. In real life, even the most motivated individuals face difficulties to sustain CLS, pressed by cultural forces, deep-rooted habits, society rules and commercial interests that encourage sedentary lifestyle, improper diet, and excessive caloric intake[77]. This raises expectations about the potential of drug alternatives to face those situations[78,79].

## Drug treatment

### Prehypertension

Prehypertension represents an intermediate stage for established SAH, and its conversion to sustained arterial hypertension is more accelerated in black individuals[8,80]. The renin-angiotensin-aldosterone system (RAAS) is frequently activated in prehypertensive individuals[81]. That suggests that the early intervention with drugs might reduce the incidence of sustained hypertension and prevent the progression of CVD.

The Trial of Preventing Hypertension (TROPHY)[13] and the Prevention of Hypertension with the Angiotensin-Converting Enzyme Inhibitor Ramipril in Patients with High-Normal Blood Pressure (PHARAO) Study[82] were the first to show that RAAS inhibitors reduce the incidence of hypertension. The TROPHY study has assessed 772 individuals with BP of 130-139/85-89 mm Hg, randomized to receive either placebo or candesartan (16 mg/day – intervention group). All individuals were instructed about CLS. After four years, a lower incidence of SAH (9.8%) was observed in the intervention group, with a 16% reduction in RR and number necessary to treat (NNT) of 11[13]. That study has been questioned regarding some methodological aspects, which might have overvalued its results. The PHARAO study has assessed 1,008 prehypertensive individuals with BP of 130-139/85-89 mm Hg, for three years, who have been randomly allocated to receive 5 mg/day of ramipril or placebo. The ramipril group showed a 34% reduction in RR in the incidence of SAH assessed by using office BP (NNT = 9) and ABPM (32.5% *vs.* 53.0%), with an increase in the incidence of cough (4.8% *vs.* 0.4%)[82]. However, if those are long-term benefits, if they prevent CV events and are cost-effective is yet to be clarified.

Current guidelines recommend CLS to all prehypertensive individuals, and drug intervention only to those with normal-high BP values at high risk, with CVD or established kidney disease, metabolic syndrome or diabetes[1], at medical discretion. It is worth noting that so far there is only evidence for the use of RAAS blockers. Recent European guidelines on hypertension have highlighted the lack of sufficient scientific evidence supporting the beginning of drug treatment for normal-high BP levels.

In face of the evidence above and the low effectiveness of CLS in the long run, the use of low doses of antihypertensive drugs to prehypertensive individuals with no CVD, but at high risk to develop sustained arterial hypertension, should be considered[83-85].

## White-coat hypertension (WCH)

The benefit of drug treatment to WCH remains undefined, because there has never been a clinical trial specifically designed to test that hypothesis. In addition, large clinical studies designed to show target-organ protection with antihypertensive treatment have never used ABPM or home BP measurements, except in small subgroups, with a small number of CV events, which have not yielded definitive conclusions.

In the lack of direct evidence, and in the presence of high or very high CV risk (concomitance of CVD or kidney disease, target-organ lesions, metabolic syndrome or diabetes), antihypertensive treatment can be considered for WCH. Thus, assessing CV risk factors and determining the risk of individuals with WCH are required for customized decision making about their antihypertensive treatment[86].

Those patients should be followed up by using ABPM or home BP measurements.

## Masked hypertension (MH)

There is plenty of scientific evidence of the negative impact of MH on CV morbidity and mortality that justify identifying and treating those patients similarly to office hypertensive patients[42].

Clinical studies on patients with MH demonstrating the relationship between BP decrease and CV risk reduction still lack. The beginning of drug treatment for patients with MH is based on the fact that they actually have out-of-office hypertension, with CV risk similar to that of untreated hypertensives[50,87].

Patients with MH should be stratified and treated similarly to conventional hypertensives[50]. The efficacy of antihypertensive treatment should be assessed by using out-of-office BP measurement.

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