White Coat and Masked Hypertension in Chronic Kidney Disease: Importance of the Difference Between Office and Out-of-Office Blood Pressure Measurements

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Combined use of office and out-of-office blood pressure (BP) measurements allows identification of a number of specific BP patterns, including conditions characterized by discrepant levels of office and out-of-office BP, the latter assessed through either home or 24h ambulatory BP monitoring. In untreated patients, these conditions are defined as white coat hypertension (WCH, elevated office and normal out-of-office BP), or masked hypertension (MH, normal office and elevated out-of-office BP), respectively. In treated patients, these conditions are defined as white coat uncontrolled hypertension (with uncontrolled office and normalized out-of-office BP), and masked uncontrolled hypertension (with normalized office and uncontrolled out-of-office BP in spite of treatment), respectively (Figure and Table). These different hypertension phenotypes are increasingly acknowledged to have clinical relevance, often leading to diagnostic failure and over- or undertreatment, respectively.[1,2] The 2013 European Society of Hypertension/European Society of Cardiology Guidelines were the first to recommend considering treatment of MH,[3] because of its clinical significance and the accumulated evidence showing the overall negative impact of MH on cardiovascular prognosis (close to that of sustained hypertension).[4–9] The clinical relevance of WCH seems more controversial, with cross-sectional studies on the association between WCH and markers of organ damage yielding conflicting results. While some studies suggested that WCH is a "benign" condition, which should be identified only to avoid unnecessary antihypertensive treatment, other studies provided evidence of similar prevalence of organ damage in WCH as in sustained hypertension. Indeed, the incidence of cardiovascular events in subjects with WCH has been alternatively reported to be as low as in normotensive subjects, as high as in hypertensive patients, or intermediate between the 2 populations. However, the reproducibility of these findings, often based on a single ABPM and a single office BP measurement, is far from being optimal.[10] Indeed, data provided by population-based studies, at variance from those reported in a number of small studies, support the view that WCH is not an entirely benign condition, and have consistently shown that subclinical organ damage (ie, increase in left ventricular mass index and in carotid intima-media thickness) is greater in WCH than in true normotensives.[11,12,13] Moreover, the data provided by the PAMELA (Pressione Arteriosa Monitorate E Loro Associazioni) population have shown that WCH is associated with a number of metabolic and blood pressure–related risk factors that lead to an increased overall cardiovascular risk profile as compared with true normotensive subjects. They have also shown that WCH is associated with a much greater risk of developing conditions that further increase cardiovascular risk, such as diabetes mellitus, office and ambulatory hypertension, and left ventricular hypertrophy. Available evidence thus indicates that, although WCH is associated with a lower risk of cardiovascular morbidity and mortality than true hypertension, it carries an increased risk as compared with sustained normotension.[10]

The recent 2017 US guidelines have made a major step forward in this field, by recommending that these different hypertension patterns should be identified among untreated and treated individuals, and that treatment decisions should be based on out-of-office BP (ambulatory or home),[14] an indication further supported by the 2018 European Society of Cardiology/European Society of Hypertension Guidelines.[15] These guidelines, in addition to promoting a larger use of out-of-office BP monitoring to manage these

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2019;8:e012299. DOI: 10.1161/JAHA.119.012299.

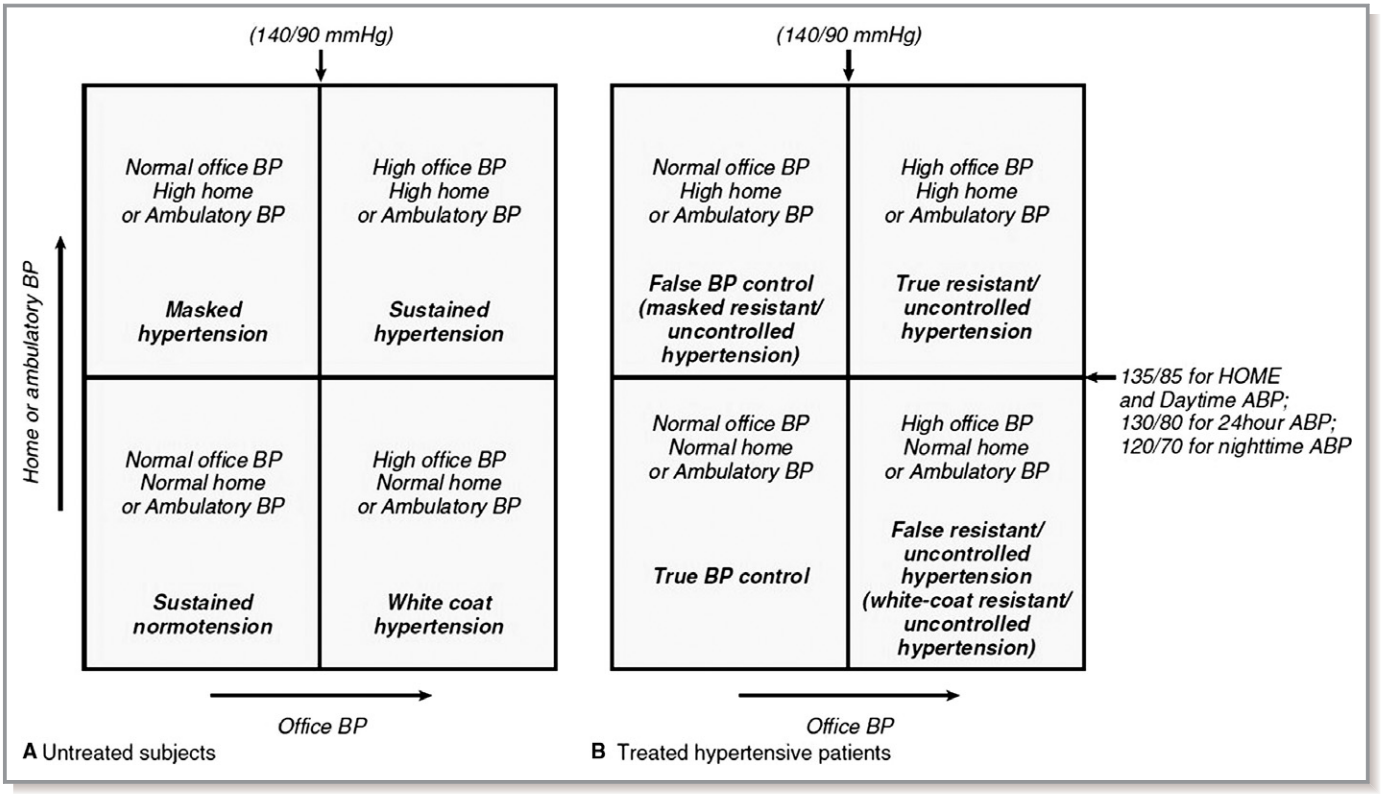

Figure. Definition of different blood pressure (BP) phenotypes, based on variable combination of office, ambulatory (A) or home BP levels in untreated subjects (**A**) and in treated hypertensive patients (**B**), respectively. Reprinted from Parati et al[13] with permission. Copyright ©2016, Wolters Kluwer Health, Inc. ABP indicates ambulatory blood pressure.

conditions, have recommended linking the decision to treat these patients to the assessment of individual levels of cardiovascular risk. The recommendation to focus on out-of-office BP appears to be of particular relevance in blacks, who are characterized by higher levels of office BP and prevalence of hypertension than whites. In these individuals, arterial hypertension starts earlier and is associated with higher cardiovascular risk, with a higher prevalence of nocturnal hypertension and nondipping BP pattern than in whites.[16] Thus they represent a population of particular interest for investigating the clinical role of WCH and MH, as they show a high prevalence of these conditions, associated with the abovementioned alterations of nocturnal BP behavior and a high prevalence also of renal damage.[17] Based on these data, a previous report of the JHS (Jackson Heart Study) suggested adoption of higher BP normality thresholds for black subjects over 24 hours, daytime and nighttime,[18] which might affect the prevalence of WCH and MH in these individuals.

Use of out-of-office BP to identify WCH and MH phenomena is particularly important in patients with chronic kidney disease (CKD),[13,19,20] who are characterized by a high prevalence of hypertension with marked alterations in their 24-hour BP profile, a reduced BP dipping at night, and a high prevalence of WCH and MH, as acknowledged by a consensus document published by the American Society of Hypertension and the American Society of Nephrology.[20]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Ku et al[21] offer additional information on the prevalence and prognostic relevance of WCH and MH-related phenomena in black patients with CKD.[21] Their analysis included 610 participants of the AASK (African American Study of Kidney Disease and Hypertension) Cohort Study who had clinic BP and ambulatory BP measured in a relatively short time. The association of the absolute difference between clinic systolic BP (SBP) and awake or 24-hour SBP with death and end-stage renal disease was assessed. The authors found a U-shaped association of the clinic–ambulatory SBP difference with risk of death, but not with end-stage renal disease. A significant increase of both a positive and a negative office SBP–awake SBP difference was associated with a trend towards higher (adjusted) mortality risk as compared with patients with more similar office and ambulatory BP levels (adjusted hazard ratio 1.84; 95% CI 0.94–3.56). The increased risk of mortality associated with a larger difference between office and ambulatory BP characterized untreated/treated black patients with CKD when affected by BP patterns reflecting either WCH/white coat

uncontrolled hypertension (identified by a positive office–ambulatory SBP difference) or MH/masked uncontrolled hypertension (identified by a negative office–ambulatory SBP difference). This association was still evident even after adjusting for office or ambulatory BP levels, thus supporting the clinical value of the office–ambulatory BP difference independently from a diagnosis of hypertension, based on office or out-of-office BP levels considered separately.

These results appear to be particularly important, given that in the CKD population, ≈10% to 30% of patients are reported to have WCH, and ≈30% to 60% of them have MH,[13,19,20] thus strongly supporting use of out-of-office BP monitoring, in particular of 24-hour ABPM, in these patients. This study also supports previous evidence that not only MH carries a high risk of cardiovascular events, but also WCH cannot be regarded as an entirely innocent phenomenon, in particular in black CKD patients. The practical implications of these findings is that, even in the presence of WCH, patients with CKD who exhibit a large difference between office and ambulatory BPs may need close follow-up and intensive cardiovascular risk reduction, because this BP condition appears to be associated with an elevated mortality risk during long-term follow-up.

This study, in spite of the interesting points it presents, is not free from limitations, as acknowledged by the authors themselves. First, the authors should have used the difference between office BP and 24-hour ABP as the primary predictor of outcome, rather than the difference between office BP and awake BP, given the known high prevalence of nighttime BP elevation in black subjects with CKD, which cannot be considered when focusing on daytime ABP levels only. Second, the terminology used in this article sometimes needs a proper interpretation, in particular when the authors refer to a positive or negative office–ABP difference by using the terms “white coat effect” or “masked effect,” respectively. There is indeed clear evidence that a difference between office and ABP levels reflects a more complex combination of factors, affecting both office BP and ABP levels, than just the emotional impact on office BP of a visit by a physician, which is responsible for the “true” white coat effect.[12] Third, in this article, an isolated increase in the positive difference between office and ambulatory diastolic BP was not associated with death, whereas an isolated increase in the negative difference between office and ambulatory diastolic BP was. Such a discrepant behavior between systolic and diastolic BP when comparing office and out-of-office values is not adequately discussed in the article by Ku et al[21] and might need further investigation. Fourth, as acknowledged by the authors in their study limitations sessions, this study focused on data obtained in hypertensive black patients with CKD, which do not permit generalization of its results to all CKD patients with hypertension. Finally, only baseline ABPM data were considered, which may have introduced some inaccuracy in the estimates because of the limited reproducibility of a single ambulatory BP recording. In spite of these limitations, however, the study by Ku et al[21] is able to clearly demonstrate that the magnitude of the difference between office and

Table. Definition of White-Coat and Masked Hypertension Phenomena

White-coat (or isolated office) hypertension
Untreated individuals with elevated office BP ≥140/90 mm Hg
and 24-h ABP <130/80 mm Hg
and Awake ABP <135/85 mm Hg
and Sleep ABP <120/70 mm Hg
or Home BP <135/85 mm Hg
Masked hypertension
Untreated individuals with office BP <140/90 mm Hg
and 24-h ABP ≥130/80 mm Hg
and/or Awake ABP ≥135/85 mm Hg
and/or Sleep ABP ≥120/70 mm Hg
or Home BP ≥135/85 mm Hg
White-coat uncontrolled hypertension
Treated individuals with elevated office BP ≥140/90 mm Hg
and 24-h ABP <130/80 mm Hg
and Awake ABP <135/85 mm Hg
and Sleep ABP <120/70 mm Hg
or Home BP <135/85 mm Hg
Masked uncontrolled hypertension
Treated individuals with office BP <140/90 mm Hg
and 24-h ABP ≥130/80 mm Hg
and/or Awake ABP ≥135/85 mm Hg
and/or Sleep ABP ≥120/70 mm Hg
or Home BP ≥135/85 mm Hg
• Diagnoses require confirmation by repeating ambulatory or home BP monitoring within 3–6 months, depending on the individual’s total cardiovascular risk • Ambulatory BP values obtained in the office during the first or last hour of a 24-h recording may also partly reflect the white-coat effect (“white-coat” window) • Patients with office BP <140/90 mm Hg, 24-h BP <130/80 mm Hg, awake BP <135/85 mm Hg but sleep BP ≥120/70 mm Hg should be defined as having “Isolated Nocturnal Hypertension,” to be considered as a form of masked hypertension

ABP indicates ambulatory blood pressure; BP, blood pressure.
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ambulatory SBP has prognostic relevance and should be assessed, at least in black hypertensive patients with CKD, on top of measuring average levels of office and ambulatory BP. It also emphasizes that both office and ambulatory BP are important and carry prognostically relevant complementary information.

These data provide additional support to what has been recently recommended by both US and European Guidelines, ie, the need to expand the use of out-of-office BP in daily practice. However, in order to more consistently support the clinical usefulness of ABPM and home BP monitoring in the routine assessment of CKD patients, as well as in a general population, we would need randomized intervention outcome trials aimed at comparing the impact on intermediate and hard end points of a hypertension management based on office or on out-of-office BP measurements, respectively. This would also allow identification of outcome-based thresholds for hypertension diagnosis and targets for treatment not only for office BP but also for out-of-office BP, a piece of information yet currently missing. It would also allow the design of treatment algorithms aimed at achieving these appropriately defined targets for each specific, office and out-of-office BP-based group, as well as exploration of their impact on clinical outcomes. The currently running MASTER (Masked-uncontrolled hypertension management based on office BP or on out-of-office [ambulatory] BP measurement) study (NCT02804074),[22] focusing on patients with masked uncontrolled hypertension, is expected to provide information aimed at finally clarifying whether a management strategy based on out-of-office BP measurements might offer a greater benefit in terms of prevention or regression of organ damage and prevention of cardiovascular events than a management strategy based only on office BP readings.[22] The MASTER study might thus help assessing the actual value of out-of-office BP monitoring in improving cardiovascular protection. Until such data become available, it would nevertheless not seem sensible to completely disregard either subjects with MH having elevated home or ambulatory BP (daytime and/or nighttime), just because their BP in the office is not increased, or subjects with WCH or white coat uncontrolled hypertension, having office BP elevated, just because their out-of-office BP is not increased. These subjects certainly deserve carefull follow-up over time and interventions focused on lifestyle changes. Whether they would also need pharmacological treatment has been critically addressed by both US and European hypertension guidelines,[14,15] but the level of evidence supporting such recommendations is low (level C), and further investigations in the same line explored by the MASTER study are still needed.

Disclosures

None.

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Key Words: Editorials • ambulatory blood pressure monitoring • end-stage renal disease • hypertension, kidney • mortality