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REVIEW SERIES

Is white-coat hypertension a harbinger of increased risk?

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White-coat hypertension is defined by elevated office and normal out-of-office blood pressure (home or ambulatory) in untreated subjects. This condition is common in clinical practice and requires appropriate work-up for detection and management. Many studies have examined the relationship between white-coat hypertension and cardiovascular risk but with marked heterogeneity in the definitions and methodology applied. Thus, the results have been inconsistent leading to confusion in scientific research and clinical practice. Some but not all the relevant studies suggested that white-coat hypertension is associated with subclinical target-organ damage, yet the cross-sectional design of these studies and the fact that these indices are only surrogate end points do not allow firm conclusions to be drawn. In recent years, longitudinal studies have examined the prognostic significance of white-coat hypertension in terms of cardiovascular morbidity and mortality. Most of them indicate that white-coat hypertensive compared with normotensive subjects present a moderate—in most cases not significant—increase in risk. Meta-analyses of raw data from large databases, such as the International Database on Ambulatory blood pressure and Cardiovascular Outcomes (IDACO) and the International Database on HOme blood pressure in relation to Cardiovascular Outcomes (IDHOCO) allowed separate powered analyses in untreated subjects and provided a clearer picture regarding the modest risk associated with white-coat hypertension, especially in the long term. White-coat hypertension is regarded as an intermediate phenotype between normotension and hypertension associated with increased risk of developing sustained hypertension, and therefore requires regular follow-up using nonpharmacological measures.
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DEFINITION OF THE WHITE-COAT HYPERTENSION

The definition of white-coat hypertension was first introduced by T Pickering[1] in 1988 as an elevated office blood pressure and normal daytime ambulatory blood pressure. Since then, the traditional definition according to the 2013 European Society of Hypertension guidelines is based on an elevated office blood pressure ($\geqslant$140/90 mm Hg) with normal out-of-office blood pressure values ($<$135/85 mm Hg), based on either daytime ambulatory or home blood pressure monitoring.[2] It should be noted, however, that there is only a moderate agreement in the classification of white-coat hypertensive subjects detected by ambulatory or home blood pressure monitoring, which is attributed to inherent differences of the methods as well as their imperfect reproducibility.[3,4]

Owing to the increased interest in the prognostic value of the nighttime ambulatory blood pressure in terms of cardiovascular risk prognosis, it has been suggested that the nocturnal blood pressure should not be ignored when white-coat hypertension is defined on the basis of ambulatory blood pressure monitoring and that all the aspects of the 24-h blood pressure profile should be taken into account.[5] Thus, for the definition of white-coat hypertension a normal 24 h ambulatory blood pressure recording is now required, with average 24 h blood pressure $<$130/80, daytime $<$135/85 and nighttime $<$120/70 mm Hg (instead of normal daytime blood pressure only).[5]

Another issue to be noted is that the term white-coat hypertension (or more correctly isolated office hypertension) refers to untreated subjects only. The white-coat effect is a different term referring to the rise in blood pressure in the office compared with ambulatory or home blood pressure measurements, regardless of the absolute levels of blood pressure (higher or lower than the hypertension threshold for each measurement method) or the use of antihypertensive treatment.[5–7] Office blood pressure at least 20/10 mm Hg (systolic and/or diastolic) higher than awake ambulatory blood pressure has been designated as 'clinically important' white-coat effect.[5–7]

PREVALENCE AND FEATURES

Population studies showed the prevalence of the white-coat hypertension at about 10–15%, whereas this phenomenon occurs in

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20–30% of subjects with elevated office blood pressure.[2,7,8] Although there are no definite diagnostic characteristics indicating the presence of white-coat hypertension, some factors are associated with an increased likelihood of the phenomenon. More specifically, white-coat hypertension occurs more often in women, older adults and nonsmokers, and less frequently in subjects with lower office blood pressure—especially when based on repeated visits—as well as in subjects with clinic hypertension and absence of target-organ damage.[2,7–10] Indeed, previous studies have shown that the age-related increase in blood pressure levels is much steeper when office rather than ambulatory or home blood pressure measurements are taken into account.[11] In addition, the prevalence of the white-coat hypertension decreases from 55% in clinic hypertension grade 1 to 10% in grade 3.[12] Moreover, some studies have suggested that white-coat hypertension may be associated with an adverse metabolic profile. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, untreated subjects with white-coat hypertension had a higher risk of new-onset diabetes compared with normotensive individuals during a 10-year follow-up.[13]

It should be noted, however, that despite the suggested features associated with the white-coat hypertension, it is still very difficult to indicate with accuracy who should be suspected for this phenomenon in routine clinical practice.

WHITE-COAT HYPERTENSION AND TARGET-ORGAN DAMAGE

The association of the white-coat hypertension with preclinical target-organ damage has been extensively studied with conflicting results. Researchers have focused on several indices of end organ involvement, such as echocardiographic left ventricular mass index (LVMI), common carotid intima-media thickness (cIMT), pulse wave velocity (PWV) and urinary albumin. The vast majority of these studies have cross-sectional design but with considerable methodological differences. Most researchers used ambulatory rather than home blood pressure monitoring as reference out-of-office blood pressure measurement method for defining subjects with white-coat hypertension. However, there is a large heterogeneity regarding the component of the ambulatory blood pressure profile (average 24 h or daytime) and the cutoff values used to identify subjects with white-coat hypertension. In addition, studies differ in size and synthesis of the populations selected for participation and in the confounders considered in the statistical analysis of the data.

Regarding the cardiac involvement, many studies associated white-coat hypertension with an intermediate stage of left ventricular hypertrophy. In particular, seven[14–20] out of eleven[14–24] relevant studies identified, demonstrated that LVMI is greater in subjects with white-coat hypertension than in normotensive controls. Moreover, in most studies it appears that the subclinical heart damage in white-coat hypertension is less than that in sustained hypertension.[16,18–21,23,24] In the PAMELA study including 1637 untreated subjects, Sega *et al.*[14] suggested that those with isolated office hypertension, LVMI wall thickness and left ventricular hypertrophy were on average less than in subjects with both office and ambulatory or home blood pressure elevation, but greater than in those with normal office and out-of-office (ambulatory or home) blood pressure. However, there are studies with negative results regarding the presence of left ventricular hypertrophy in white-coat hypertension.[21–24] For example, a study by Kotsis *et al.*[22] in 1535 untreated subjects of whom 18% were classified as having white-coat hypertension did not show a significant difference in LVMI between white coat and normotensive subjects.

Results from studies that investigated the association between white-coat hypertension and vascular damage assessed by cIMT have been inconclusive. Six studies reported higher cIMT values in subjects with white-coat hypertension compared with normotensive subjects.[15,25–29] In addition, four[26–29] of them indicated that carotid structure changes were similar in subjects with white-coat hypertension and sustained hypertension, whereas other studies did not confirm this finding. In fact, other groups have demonstrated that the severity of the carotid involvement in white-coat hypertension appears to be lower compared with subjects with masked[30,31] or sustained[15,18,21,30–32] hypertension. Puato *et al.*[27] in a 5-year prospective study of 74 untreated subjects with mild hypertension and 20 normotensive subjects showed that subjects with white-coat hypertension presented higher cIMT values and faster progression compared with normotensive participants, in a similar pattern compared with those with sustained hypertension. In addition, Fukuhara *et al.*[25] in a general population sample of 2915 subjects (both treated and untreated, 7% white-coat hypertension classified on the basis of home blood pressure monitoring) demonstrated higher cIMT values in white coat compared with normotensive subjects. On the other hand, several investigators failed to demonstrate higher cIMT values in subjects with white-coat hypertension compared with normotensive individuals.[18,21,22,30,31,33] In fact, two of these studies conducted in large population-based samples of subjects monitored by self-measurements of blood pressure at home did not identify the presence of significant differences in cIMT between white-coat hypertensive and normotensive subjects.[30,33]

The relationship between white-coat hypertension and increased PWV also remains controversial. Using home blood pressure measurements, Matsui *et al.*[31] demonstrated that PWV rises moving from normotension to white-coat hypertension, masked hypertension and sustained hypertension, whereas using daytime ambulatory blood pressure monitoring Andrikou *et al.*[34] showed that subjects with white-coat hypertension exhibit higher PWV values than normotensive subjects, equal to masked hypertensive patients but lower than patients with sustained hypertension. On the contrary, other investigators did not detect differences in arterial stiffness indices in white-coat hypertensive compared with normotensive subjects.[33,35]

Regarding the indices of renal involvement in subjects with white-coat hypertension, findings appear to be more uniform. More specifically, the majority of studies showed that urinary albumin did not differ significantly between individuals with white-coat hypertension and normotension.[15,19,20,23,36] However, Høegholm *et al.*[37] in a study of 411 subjects (27% with white-coat hypertension), reported that urine albumin excretion in white-coat hypertension detected by ambulatory blood pressure monitoring was intermediate between normotension and sustained hypertension.

PROGNOSTIC VALUE OF WHITE-COAT HYPERTENSION IN TERMS OF CARDIOVASCULAR EVENTS

Despite 25 years of research in white-coat hypertension, its clinical relevance in terms of prognosis remains rather uncertain. There are several longitudinal studies that addressed this research question; however, there is a large heterogeneity regarding the population characteristics, the inclusion or not of treated participants, the protocol for office blood pressure measurement, the reference out-of-office blood pressure monitoring method and the cutoff values used, the duration of the follow-up etc. Recent meta-analyses provide a summarized picture and reveal a trend toward a marginal nonsignificant increase in cardiovascular risk in white-coat

hypertensive *vs.* normotensive subjects, but their findings should be interpreted in light of their limitations and the methodological details. In fact, some of the methodological issues that might affect the conclusions and should be taken into account include the following: (i) the separation of untreated subjects from treated ones, since white-coat hypertension referring to untreated individuals is different from the white-coat effect seen in treated individuals, (ii) the type of the out-of-office blood pressure monitoring method used, since ambulatory and home blood pressure monitoring do not appear to be fully interchangeable methods, and (iii) the lack of information on office and out-of-office blood pressure levels and the use of antihypertensive drug treatment during follow-up.

Verdecchia *et al.*[38] performed the first meta-analysis of individual data from four prospective cohort studies from the United States, Italy and Japan. The total sample included 5955 subjects (67% with sustained hypertension, 7% with white-coat hypertension) and daytime ambulatory blood pressure monitoring was used as the reference out-of-office blood pressure measurement method (cutoff 130/80 mm Hg). It should be noted that in three of these studies, subjects on antihypertensive medications were withdrawn from medications for a minimum of 2 weeks before baseline ambulatory blood pressure monitoring. The adjusted hazard ratio (HR) for stroke was 1.15 (95% confidence intervals (CI): 0.61, 2.16) for white-coat hypertensive *vs.* normotensive subjects for a median follow-up of 5.4 years. However, after the sixth year of follow-up, the incidence of stroke tended to increase in the white-coat hypertensive subjects, and the corresponding hazard curve crossed that of the sustained hypertensive patients by the ninth year of follow-up, suggesting that in the long term white-coat hypertension might not be a benign condition in regard to stroke risk. This finding could be attributed, at least in part, to the fact that some subjects with white-coat hypertension might have developed sustained hypertension during follow-up. It should be noted, however, that this study did not overcome the problems of measurement error, response bias and confounding, and was underpowered to conclude that white-coat hypertensive subjects have an increased risk of stroke after 9 compared with 6 years of follow-up.[39]

Fagard and Cornelissen[8] conducted another meta-analysis based on aggregate data from six studies including 10 924 subjects derived from population samples, and from primary and specialist care settings. All the studies used daytime ambulatory blood pressure monitoring as reference except two that used home blood pressure monitoring. In the first one, home blood pressure was derived from the average of a single measurement in the morning and another in the evening,[40] and in the second from the average of three blood pressure measurements in the morning and three in the evening during a 4-day period.[41] The overall adjusted HR for aggregates of fatal and nonfatal cardiovascular events was 1.12 (95% CI: 0.84, 1.50) for white-coat hypertensive *vs.* normotensive subjects for an average follow-up of 8 years. Again, a significant limitation was the inclusion of subjects receiving antihypertensive drug treatment.

Hansen *et al.*[42] performed a meta-analysis of individual data from 7030 subjects (10.6% with white-coat hypertension) from 4 population studies in Denmark, Belgium, Japan and Sweden (2007 International Database on Ambulatory blood pressure and Cardiovascular Outcomes (IDACO)) with a median follow-up of 9.5 years. Daytime ambulatory blood pressure was used as reference out-of-office blood pressure measurement method and the cutoff value of 135/85 mm Hg was used for the classification. One of the major advantages of this study was the separate analyses of treated and untreated subjects. More specifically, among 5510 initially untreated subjects the adjusted HR for cardiovascular events was 1.25 (95% CI: 0.86, 1.82) for white-coat hypertensive *vs.* normotensive subjects, whereas the respective HR for treated subjects ($n = 1520$) was somewhat lower at 1.15 (95% CI: 0.76, 1.75). By censoring analysis at 6, 9 and 12 years, the adjusted HR for the composite end point between white-coat hypertensive (both treated and untreated) and normotensive subjects was 1.08 (95% CI: 0.61, 1.88), 1.20 (95% CI: 0.86, 1.69) and 1.30 (95% CI: 1.01, 1.68), respectively.

In the context of separate analyses in untreated subjects, Pierdomenico *et al.*[43] performed an updated meta-analysis of aggregate data from studies including untreated subjects at baseline or from studies performing separate analysis for untreated or treated subjects. More specifically, five studies were eligible for the assessment of the white-coat hypertension-related cardiovascular risk in initially untreated subjects (1279 white-coat hypertensive and 2391 normotensive subjects). In four of these studies, daytime ambulatory blood pressure monitoring was used as the reference out-of-office blood pressure measurement method, whereas in one 24 h ambulatory blood pressure monitoring was applied. The overall adjusted HR was 0.96 (95% CI: 0.65, 1.42) for white-coat hypertension *vs.* normotension, and this ratio did not change when analysis was repeated according to the normotensive population sample used as control (different or same) and the duration of follow-up.

Franklin *et al.*[44] recently examined the relevance of white-coat hypertension in older persons with isolated systolic hypertension by using the updated population-based 11-country IDACO database. Daytime ambulatory blood pressure with cutoff 135/85 mm Hg was used for the classification of the participants. During a median follow-up of 10.6 years, there were a total of 655 fatal and nonfatal cardiovascular events among 7295 participants. The analysis was stratified by treatment status and in the untreated group subjects with white-coat hypertension ($n = 334$) were at similar risk as those with normotension ($n = 5271$) (adjusted HR: 1.17 (95% CI: 0.87, 1.57)).

A recent meta-analysis investigated the prognostic value of white-coat hypertension in 6458 participants enrolled in the International Database on HOme blood pressure in relation to Cardiovascular Outcomes (IDHOCO) from five populations.[45] Home blood pressure monitoring was performed as the reference method for out-of-office blood pressure evaluation. During a median follow-up of 8.3 years in untreated subjects ($n = 5007$) the cardiovascular risk was higher in white-coat hypertension *vs.* normotension (adjusted HR: 1.42, 95% CI: 1.06, 1.91), whereas in treated patients ($n = 1451$) the cardiovascular risk did not differ between subjects with white-coat hypertension and those with normotension (adjusted HR: 1.16, 95% CI: 0.79, 1.72).[45]

The abovementioned data suggest that the treatment status might affect the prognostic value of the white-coat hypertension. First, the inclusion of treated individuals or patients with cardiovascular disease in the normotensive comparator group—which has been the case in some of the above studies—may have masked the true difference between normotensive and white-coat hypertensive subjects. On the other hand, treated subjects with white-coat effect are usually more aggressively treated—on the basis of their elevated office blood pressure—which might explain at least in part their more favorable prognosis. It is noteworthy that untreated subjects with white-coat hypertension appear to present a marginal increase in future cardiovascular risk compared with untreated normotensive subjects, as suggested by the meta-analyses of the IDACO and

IDHOCO databases.[42,45] A recent review also provided information on the cardiovascular risk according to cross-classification by office and daytime ambulatory blood pressure and treatment status by using a low-risk comparator group (defined by the absence of prior cardiovascular events, hypertensive target-organ damage, significant cardio-metabolic risk factors, masked hypertension and antihypertensive drug treatment).[7] The authors concluded that untreated subjects with white-coat hypertension present equal cardiovascular risk compared with the low-risk group, but the risk increased in the presence of associated cardio-metabolic risk factors.[7] On the other hand, unnecessarily treated white-coat hypertensive subjects were at similar risk as the low-risk group.[7] Thus, conclusions should be drawn from analyses conducted exclusively in untreated subjects. The slight increase in cardiovascular risk in the white-coat hypertensive subjects could be attributed to the following findings: (i) there is a linear relationship between blood pressure levels and cardiovascular risk[46] and it is known that white-coat hypertensive subjects tend to present higher out-of-office blood pressure values compared with normotensive[42,45] and (ii) previous studies have shown that white-coat hypertensive subjects present an increased risk of developing sustained hypertension in the future.[47,48] The adjusted risk of subjects with white-coat hypertension for progression to home hypertension during an 8-year follow-up was significantly threefold higher than for subjects with sustained normotension.[48] Another issue deserving attention is that the findings might differ according to the out-of-office blood pressure monitoring method used for diagnosis. Indeed, previous studies have shown that ambulatory and home blood pressure monitoring methods are not fully interchangeable in terms of classification in the blood pressure categories. The findings of the IDACO (based on ambulatory blood pressure monitoring) and the IDHOCO (based on home blood pressure monitoring) analyses imply that these methods might differ in terms of prognosis in the case of white-coat hypertension. On the other hand, the PAMELA general population study defined the blood pressure groups on the basis of 24 h ambulatory blood pressure and on the basis of home blood pressure monitoring and found similar results in terms of the white-coat hypertension-related cardiovascular risk.[40] However, these results were neither adjusted nor stratified for antihypertensive treatment. Later reports from the PAMELA study providing results adjusted for potential confounders showed that among subjects with white-coat hypertension, those with low home and ambulatory blood pressure had lower cardiovascular mortality than those with only one of them being low, suggesting a complementary rather than competitive role of the two methods.[49]

CONCLUDING REMARKS

The accurate diagnosis of white-coat hypertension is based on repeated elevated office blood pressure values in association with normal home or ambulatory (daytime and nighttime) blood pressure in untreated subjects. The available evidence suggests that many but not all subjects with apparent white-coat hypertension represent an intermediate phenotype between normotension and hypertension. Current guidelines recommend frequent follow-up of white-coat hypertensive subjects in order to identify those who develop sustained hypertension and/or have metabolic abnormalities, and therefore require treatment *vs.* those who remain with white-coat hypertension without increased risk and do not require antihypertensive therapy.

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