American Versus European Hypertension Guidelines: The Case of White Coat Hypertension

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BACKGROUND
The impact of the 2017 American College Cardiology/American Heart Association guidelines on reclassification of white coat hypertension (WCH) and white coat uncontrolled hypertension (WUCH) phenotypes has not been thoroughly investigated, so far. The aim of the present analysis was to compare the prevalence rates of WCH and WUCH according to either 2018 European Society Hypertension/European Society Cardiology and 2017 ACC/AHA hypertension guidelines.

METHODS
A large database of individual 24-hour ambulatory blood pressure (BP) recordings from untreated and treated hypertensive individuals with office BP ≥140 and/or 90 mm Hg was analyzed.

RESULTS
As many as 3,223 (39% men) out of 7,353 (47% men) fulfilled diagnostic criteria for WCH ($n = 1,281$) and WUCH ($n = 1,942$) according to the 2018 ESH/ESC guidelines (mean 24-hour BP <130/80 mm Hg), the prevalence rate being 17.4% and 26.4%, respectively. The corresponding figures according to the 2017 ACC/AHA guidelines (mean 24-hour BP <125/75 mm Hg) were 15.6 and 9.4%, respectively. Thus, a total of 1,378 patients (42.7%) either defined as WCH and WUCH by ESH/ESC guidelines, were classifiable as untreated sustained and uncontrolled sustained hypertensives by ACC/AHA guidelines.

CONCLUSIONS
The ACC/AHA reclassification of patients with office BP ≥140/90 mm Hg leads to a marked decrease in the prevalence of WCH/WUCH. This may have relevant clinical implications because the prognostic significance of these phenotypes is often ignored in clinical practice and, consequently, contributes to the high burden of cardiovascular diseases worldwide.

Keywords: ambulatory blood pressure; blood pressure; guidelines; hypertension; white coat hypertension; white coat uncontrolled hypertension

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Starting from the original description by Pickering *et al.*,[1] published more than 30 years ago, growing attention has been paid to white coat hypertension (WCH) a condition in which diagnosis of hypertension by office measurements is not confirmed by ambulatory or home blood pressure (BP) monitoring. Originally limited to untreated individuals, this definition has more recently been extended also to individuals regularly taking BP lowering drugs (i.e. white coat uncontrolled hypertension or WUCH).[2]

In the last decades, several cross-sectional and longitudinal studies as well as their meta-analyses have been addressing the clinical and prognostic significance of WCH targeting a variety of outcomes such as metabolic alterations, subclinical cardiac and extracardiac target organ damage, cardiovascular morbidity and mortality as well as all-cause death.[3–5] In contrast to previous view, available evidence nowadays supports the notion that WCH is not an innocent condition; uncertainties, however, persist about the prognostic role and, more importantly, the appropriate management of this condition.[6]

Some authors, indeed, have suggested that cardiovascular risk associated with WCH is similar to that of sustained normotensive individuals,[7] whereas other researchers have documented for WCH an intermediate risk between normotension and hypertension.[8] Furthermore, significant differences in cardiovascular risk between WCH and WUCH have been reported.[9]

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Finally, available data on the prevalence of these BP phenotypes are inconsistent (range from 10% to 40%), the variability being likely related to differences in the methods for out-of-office BP assessment (ambulatory vs home), protocols (single vs repeated office measurements, number/duration of home BP readings, single versus repeated ambulatory monitoring), and diagnostic ambulatory criteria (mean daytime vs mean 24-hour).[10] A further source of variability in the diagnosis of WCH is linked to the different criteria for normal office and out-of-office BP, assessed by ambulatory BP monitoring (ABPM) recommended by the 2017 the American College of Cardiology/American Heart Association (ACC/AHA) and the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) hypertension guidelines.[11,12]

On the basis of these data, considering the large ABPM database collected in our research center, we aimed to compare the prevalence rates of WCH and WUCH in adult out-patients according to either ESH/ESC and ACC/AHA hypertension guidelines and evaluate the impact of reclassification of these phenotypes according to the lower ACC/AHA ambulatory BP thresholds.

METHODS

A total of 7,353 individual 24-hour ambulatory BP recordings (ABPM) from untreated individuals with a history of hypertension and treated hypertensive individuals referred to a single out-patient hypertension center (Clinical Research Unit Meda, Istituto Auxologico Italiano and University of Milano-Bicocca) by their general practitioners during a 6-year period (from November 2013 to November 2019) with office systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg were analyzed. In each patient three sphygmomanometric BP measurements in the sitting position were recorded by trained professional nurses before the start of the ABPM recording, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively.

The three BP measurements obtained in this setting were averaged to obtain office BP. All ABPMs were performed on a working day (Monday to Friday) with an ABPM device (Spacelabs 90207) set to obtain automated BP and heart rate oscillometric readings every 20 minutes during the 24 hours. The subjects were asked to pursue their normal activities during the monitoring period with the precaution of holding the arm still at time of BP readings and going to bed no later than 11.00 PM and arising not before 7.00 AM Recordings were analyzed to obtain 24-hour, daytime (7.00 AM to 11.00 PM) and nighttime (11.00 PM to 7.00 AM) average systolic BP/diastolic BP, nocturnal systolic blood pressure decrease (%), and corresponding heart rate values. Individuals with office systolic BP <140 and/or diastolic BP <90 mm Hg, aged <18 years and/or with suboptimal ABPM recordings (<70% successful readings) were excluded from the present analysis.

Definitions

Based on office and 24-hour ambulatory BP values, individuals were classified as: (1) WCH (i.e. untreated elevated office systolic or diastolic BP and normal 24-hour ambulatory BP); (2) WUCH (i.e. treated elevated office systolic or diastolic BP and normal 24-hour ambulatory BP). Untreated and treated individuals with elevated office and 24-hour BP were classified as sustained and uncontrolled sustained hypertensives, respectively. The prevalence rates WCH and WUCH were assessed according to both European and American hypertension guidelines, namely for normal threshold values of 24-hour BP lower than 130/80 and 125/75 mm Hg, respectively. Age related prevalence of WCH/WUCH was assessed by dividing the total sample in three age strata: (1) young (18–40 years); (2) middle-aged (41–64 years); (3) elderly (≥65 years).

Statistical analysis

Statistical analysis was performed by SAS System (version 6.12; SAS Institute Inc., Cary, North Carolina, USA) and was mostly descriptive; values are expressed as means or as percentages. Mean values have been compared by Student's *t*-test for independent samples and categorical data analyzed by chi-square test or Fisher's exact test when appropriate. The *P* value <0.05 was considered statistically significant.

RESULTS

Figure 1 shows the flowchart for the selection and classification of patients according to their office and ambulatory 24-hour BP. A total of 7,353 ABPM recordings of good technical quality carried out in untreated and treated patients with office systolic BP equal or higher than 140 mm Hg and/or diastolic BP equal or higher than 90 mm Hg were analyzed in order to assess the prevalence rates of both WCH and WUCH according to criteria previously reported in the Methods. Table 1 summarizes demographic and clinical data of the total population as well as of WCH and WUCH subgroups according to both ESH/ESC and ACC/AHA guidelines.

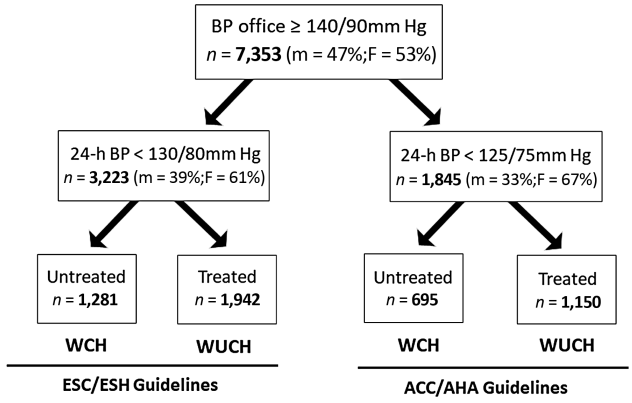

Figure 1. Flowchart summarizing the selection and classification of patients with untreated and treated office blood pressure (BP) >140/90 mm Hg according to average 24-h BP thresholds recommended by the 2018 ESH/ESC and the 2017 ACC/ACC guidelines.

Table 1. Demographic variables of the study population data from the total sample, white coat hypertension (WCH) and white coat uncontrolled hypertension (WUCH), defined by ESH/ESC and ACC/AHA guidelines

Variables	Total population	WCH ESH/ESC	WCH ACC/AHA	WUCH ESH/ESC	WUCH ACC/AHA
Number	7,353	1,281	695	1,942	1,150
Female, prevalence (%)	53	61#	70	61°	67
Age 18–40 years (%)	16	14	14	3	3
Age 41–64 years (%)	40	54	52	38°	24
Age >65 years (%)	44	32	34	59°	63
Antihypertensive drugs (%)	55	—	—	100%	100%

#$P < 0.01$ WCH ESH/ESC vs WCH ACC/AHA.
°$P < 0.01$ WUCH ESH/ESC vs WUCH ACC/AHA.

ESH/ESC classification (Table 1)

As many as 3,223 (39% men) out of 7,353 (47% men) fulfilled diagnostic criteria for WCH (n = 1,281) and WUCH (n = 1,942) according to the 2018 ESH/ESC guidelines. This means that 17.4% of the patients could be classified as WCH and 26.4% as WUCH, respectively, while the remaining 57.2% had sustained hypertension (office and 24-hour BP both elevated). A gender-based analysis showed that both in WCH and WUCH subgroups women were more prevalent than men (58.1% and 60.5%, respectively). Unlike gender distribution, the frequency of WCH and WUCH across the age strata was quite different: the majority of WCH patients, indeed, were middle-aged (54%), whereas WUCH patients were more prevalent among the elderly (58%), without any difference between men and women (Figure 2).

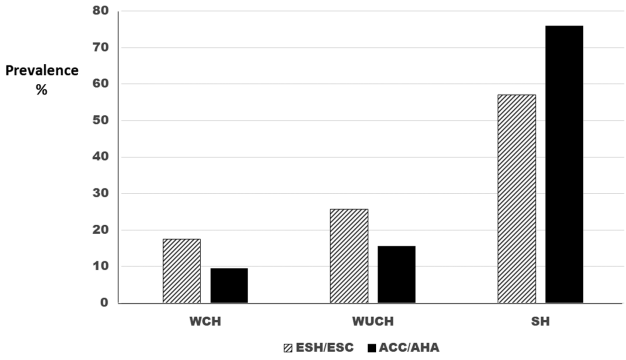

Figure 2. Prevalence rates of white coat hypertension (WCH), white coat uncontrolled hypertension (WUCH) and the sum of untreated/uncontrolled sustained hypertension (SH) according to ESH/ESC and ACC/AHA guidelines.

ACC/AHA reclassification (Table 1)

The reclassification of patients according to normal criteria for 24-hour ambulatory BP endorsed by the ACC/AHA guidelines substantially reduced the prevalence of both WCH (9.4%) and WUCH (15.6%). This means that 586 and 792 patients defined, respectively, as WCH and WUCH by the ESH/ESC guidelines, were reclassified by ACC/AHA guidelines as sustained and uncontrolled sustained hypertensive, thus reducing the prevalence of WCH by 45.8% and WUCH by 40.8%. It should be noted that according to ACC/AHA classification gender and age distribution of both WCH and WUCH were not different from ESH/ESC classification.

DISCUSSION

The present analysis, based on a large sample of patients from a single specialist out-patient hypertension center, shows that proportion of WCH and WUCH as assessed by ABPM markedly decreases, while the proportion of sustained hypertension and sustained uncontrolled hypertension increases when applying ACC/AHA ambulatory 24-hour BP thresholds instead of ESH/ESC ones. The 2017 ACC/AHA classification moved 45.8% individuals from WCH to sustained hypertension and 40.8% from WUCH to sustained uncontrolled hypertension, respectively, thus increasing the prevalence of individuals with high in- and out-of-office hypertension to 76% of the total population. Before addressing these findings in detail, some general considerations on available evidence in this clinical and research area might be useful.

The 2017 ACC/AHA hypertension guidelines modified the criteria for recognition of hypertension, using an office BP threshold of 130/80 mm Hg instead of 140/90 mm Hg which has been set for many decades as the reference value to distinguish normotensive individuals from hypertensive ones. On the contrary, the 2018 ESH/ESC guidelines have maintained the traditional 140/90 mm Hg value thus leading to a divergence in the diagnosis and treatment of arterial hypertension between the two most authoritative guidelines. In parallel, the differences in BP classification also affected the 24-hour, daytime and nighttime ABPM thresholds set at 125/75, 130/80, and 115/65 mm Hg by ACC/AHA compared to traditional values confirmed by ESH/ESC (i.e. 130/80, 135/85, and 120/70 mm Hg). The impact of the updated ACC/AHA criteria on the prevalence and control of hypertension has been assessed in surveys carried out in population-based samples and in hypertensive cohorts both in the US and Europe.[13–15]

Data from the 2011 to 2014 National Health and Nutrition Examination Survey based on 9,623 participants documented that according to the 2017 ACC/AHA and JNC7 (or ESH/ESC) guidelines, prevalence of hypertension

among US adults was 45.6% and 31.9%, respectively. The corresponding values for uncontrolled hypertension among individuals taking antihypertensive medication were 53.4% and 39.0%, respectively.[13] A Spanish survey aimed at estimating the prevalence of hypertension in 12,070 adult individuals representative of the general population, showed that implementation of ACC/AHA guidelines as an alternative to ESH/ESC ones would have resulted in a substantial increase in the prevalence of hypertension (+13%) and the number of adults requiring BP lowering drugs (+4%).[15]

On the contrary, the impact of ACC/AHA guidelines on reclassification of WCH and WUCH phenotypes is largely unknown.[16] Thus, our study adds a new piece of information on this issue by showing a consistent decrease in the prevalence of WCH (from 17% to 9%) and WUCH (from 26% to 15%) and a consequent increase in the overall prevalence of untreated sustained and uncontrolled hypertension (from 57% to 76%) by applying the recommended ACC/AHA threshold. for ambulatory BP instead of the ESH/ESC ones.

The use of more restrictive criteria in defining normal 24-hour BP pattern, when implemented in patients with office BP equal or higher than 140/90 mm Hg, tends to reduce the diagnostic inconsistency between office and ambulatory BP, typically represented by both BP phenotypes (WCH and WUCH). The clinical management of these conditions, as opposed to sustained hypertension and uncontrolled sustained hypertension, is often characterized by therapeutic inertia thus leaving patients exposed to the risk of cardiovascular complications.[17]

Some brief considerations on the different diagnostic normality ambulatory BP criteria recommended by both guidelines can be made. First, data from a large and unbiased sample of a general population showed the value of 125/79 mm Hg as the upper limit of normality for 24-hour BP (i.e. a systolic threshold identical to that proposed by ACC/AHA guidelines).[18] Second, although by definition in the normal range, the level of 24-hour systolic BP load may be a key factor in determining the enhanced cardiovascular risk also in the setting of WCH and WUCH.[19] In the Pressioni Monitorate e Loro Associazioni (PAMELA) study, compared with true normotensive participants the risk of new onset cardiovascular events was greater in WCH and WUCH with average 24-hour systolic BP over the median value (Odd ratio = 2.7, Confidence interval 1.6–4.7, $P = 0.0004$), after adjustment for potential confounders This was not the case for the subgroup with average 24-hour systolic BP below the median (Odd ratio = 1.2, Confidence interval 0.6–2.3, $P = 0.6366$) (unpublished data). Third, recent findings provided by the Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly (INFINITY) study showing that patients ≥75 years of age randomized to an intensive lowering of ambulatory BP had a reduction in accrual of white matter intensity and lower rates of cardiovascular events compared to their counterparts randomized to standard treatment support the clinical benefit of achieving tight ambulatory BP targets.[20] Taken together, these considerations allow us to suggest the decreased prevalence of WCH and white WUCH using the ACC/AHA guidelines and the corresponding increase in people classified as sustained hypertensive will not be associated with the risk of unnecessary antihypertensive treatment.

Finally, an interesting aspect of the study is the association between WCH/WUCH and female gender according to both guidelines, which suggests that the likelihood of identifying these phenotypes is much higher in women than in men. As for age, the frequency of WUCH (but not WCH) was higher in the elderly than in younger patients, this mainly due to the fact that the fraction of the subjects taking antihypertensive medications increases with age. Consequently, the presence of WUCH should be sought particularly in older women.

Several relevant limitations of our study deserve to be acknowledged. First, the present analysis has a retrospective nature and do not include detailed clinical variables (including class and number of BP lowering drugs) that may have provided useful information on clinical correlates of WCH and WUCH. Second, although a large body of evidence supports the view that BP phenotypes have a limited reproducibility and do not reflect a stable BP trait, the classification of WCH and WUCH was defined by a single ABPM recording.[2] Third, our analysis was restricted to individuals with office hypertension, and therefore cannot provide information on masked hypertension and uncontrolled masked hypertension. Fourth, it excluded individuals with stage 1 hypertension (130–139 mm Hg systolic and 80–89 mm Hg diastolic BP) according to ACC/AHA guidelines not allowing to provide data on the prevalence of WCH and WUCH in this subset, which, on the contrary, is classified as "high normal" by the ESH/ESC guidelines.

CONCLUSIONS

Our data suggest that adopting the ambulatory BP criteria recommended by ACC/AHA guidelines as an alternative to those endorsed by ESH/ESC guidelines, lead to a marked decrease in the prevalence of WCH/WUCH and to a consequent increase in the fraction of patients with untreated sustained hypertension and uncontrolled sustained hypertension. This reclassification may have a relevant impact on cardiovascular prevention at the community level, as in current practice WCH and WUCH represent a controversial and widely undertreated portion of the hypertensive population, thus contributing to the high burden of cardiovascular diseases. These BP phenotypes, in spite of the growing evidence in the opposite direction, are considered at low cardiovascular risk by the majority of healthcare professionals and this consideration favors clinical inertia.

FUNDING

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DISCLOSURE

The authors declared no conflict of interest.

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