Curr Hypertens Rep (2016) 18: 80
DOI 10.1007/s11906-016-0687-9

White Coat Hypertension: to Treat or Not to Treat?

Cesare Cuspidi[1,2,3] · **Carla Sala**[4] · **Guido Grassi**[1,5] · **Giuseppe Mancia**[1]

Published online: 27 October 2016

Abstract Definition of white coat hypertension (WCH) traditionally relies on elevated office blood pressure (BP) during repeated visits concomitant with normal out-of-office BP values, as assessed by home and/or 24-h ambulatory BP monitoring measurements. Accumulating evidence focusing on the association of WCH with target organ damage and, more importantly, with cardiovascular events indicates that the risk conveyed by this condition is intermediate between normotension and sustained hypertension. This article will review a number of issues concerning WCH with particular emphasis on the following: (1) prevalence and clinical correlates, (2) association with target organ damage and cardiovascular events, (3) therapeutic interventions. Data will refer to the original WCH definition, based on out-of-office BP determined by 24-h ambulatory BP monitoring; at variance from home BP measurement, this approach rules out the potentially confounding effect of a clinically relevant abnormal BP phenotype such as isolated nocturnal hypertension.

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

✉ Cesare Cuspidi
cesare.cuspidi@unimib.it

[1] Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy

[2] Istituto Auxologico Italiano, Milano, Italy

[3] Istituto Auxologico Italiano, Clinical Research Unit, Meda (MB), Italy

[4] Department of Clinical Sciences and Community Health, University of Milano and Fondazione IRCCS Policlinico di Milano, Milano, Italy

[5] Istituto di Ricerche a Carattere Scientifico Multimedica, Sesto San Giovanni, Milan, Italy

Keywords White coat hypertension · Organ damage · Cardiovascular prognosis · Treatment

Introduction

Over the past four decades, it has been increasingly recognized that blood pressure (BP) measured in the office by the physician may not truly represent daily BP levels out-side the medical environment because the alerting reaction elicited by doctors or nurses during office BP measurement may substantially impair the accuracy of this time-honoured BP measurement approach in estimating real-life BP levels [1••].

Combined office and out-of-office BP measurements (ambulatory BP monitoring or self-measured home BP) provide a more accurate evaluation of the BP status of a given individual and have for this reason gained an increasing application for clinical and research purposes [2]. Indeed, this comprehensive approach is now recommended also by some authoritative guidelines. For instance, UK guidelines suggest that all patients with stage 1 and 2 hypertension should have ambulatory BP monitoring (ABPM) to confirm the diagnosis of hypertension and take treatment decisions [3].

Altogether combined office and out-of-office BP measurements allow to identify four BP phenotypes: (1) true normotension (i.e. normal office and out-of-office BP), (2) sustained hypertension (elevated in-office and out-of-office BP), (3) white coat hypertension (elevated office and normal out-of-office BP) and (4) masked hypertension (normal office and elevated out-of-office BP). These BP phenotypes have been shown to substantially differ in terms of prevalence, demographics, clinical features and degree of subclinical cardiac and extra-cardiac damage as well as risk of incident cardiovascular events [4]. Among these phenotypes, the one characterized by only office BP elevation is commonly known as

"white coat hypertension" (WCH). A term which was for the first time coined by Pickering et al. [5••] to describe a subgroup of untreated individuals with a persistently elevated office BP but normal ABP values. In that pioneering paper, 21 % of 292 patients with untreated borderline clinic diastolic hypertension were found to have normal day-time ambulatory pressures and were defined as having WCH. Compared to subjects with elevated BP both in the clinic and during 24-h monitoring, those with WCH were more likely to be female, younger, less obese and more recently diagnosed with hypertension.WCH, alternatively termed "isolated clinic hypertension", is frequently diagnosed in current clinical practice, its prevalence depending on demographic and clinical characteristics of subjects as well as on methods (ambulatory or home BP measurement) and BP cutoffs used to define normal out-of-office values [6].

This article will review a number of issues concerning WCH with particular emphasis on the following: [1••] prevalence and clinical correlates [2], association with target organ damage and cardiovascular events [3], therapeutic interventions. Data will refer to the original WCH definition, based on out-of-office BP determined by 24-h monitoring; at variance from home BP measurement, this approach rules out the potentially confounding effect of a clinically relevant abnormal BP phenotype such as isolated nocturnal hypertension.

Definition, Prevalence and Clinical Aspects

Definition of WCH traditionally relies on elevated office BP (≥140 mmHg systolic BP and/or ≥90 mmHg diastolic BP) during repeated visits concomitant with BP values during day-time period below the accepted thresholds for ambulatory day-time hypertension (i.e. mean systolic BP/diastolic BP <135 and <85 mmHg in untreated individuals). Due to the clinical and prognostic relevance of nocturnal BP, the 2013 ESH position paper proposed that WCH diagnosis should be based on office readings above 140/90 mmHg and mean 24-h BP below 130/80 mmHg, thereby incorporating nocturnal BP values in the definition [7].

The majority of clinical studies have reported that WCH accounts for up to 25–30 % of individuals attending outpatient hypertension centres. Recently, the Ambulatory blood pressure Registry TEleMonitoring of hypertension and cardiovascular rISk (ARTEMIS) project, an international registry including clinic and ambulatory BP measurements in patients attending hypertension clinics in all five continents, has provided updated information on the different hypertension subtypes resulting from the combination of both BP measurements [8]. Sustained hypertension was detected in 49 % of patients; WCH (elevated clinic BP with ambulatory 24-h BP <130/80 mmHg) was approximately twofold more common than the opposite pattern masked hypertension. In particular, among 5523 untreated patients with elevated clinic BP, WCH prevalence was approximately 23 %. This condition was less common in Australia, America, and Africa, and more common in elderly and obese women. A recent sub-analysis of data collected by the Spanish ABPM Registry aimed at investigating the prevalence and reproducibility of hypertension phenotypes defined by combined clinic and ABPM measurements in 869 untreated patients showed that WCH was present in about one quarter of cases (24 %) [9]. Lower prevalence rates of WCH have been documented in numerous population-based cohorts examined across different geographic areas and ethnic groups.

In the PAMELA Study (Pressioni Arteriose Monitorate E Loro Associazioni), an epidemiologic study designed by our research group with the original purpose to determine normal values of home and ambulatory BP in the general population, 2051 individuals aged between 25 and 74 years, randomly selected from the residents in Monza (Italy) underwent sphygmomanometric, home and ABP measurements, blood and urine sampling, standard 12-lead electrocardiogram and echocardiogram examination. Among 1657 untreated participants, WCH prevalence ranged from 9 to 12 %, depending on whether out-office normotension was defined by home BP (<132/83 mmHg) or 24-h ABP monitoring (<125/79 mmHg), respectively [10]. In a community-based study conducted in Taiwan by Sung et al. [11], including a total of 1257 never-treated volunteers invited to participate a comprehensive cardiovascular survey, including carotid ultrasonography, echocardiography, 24-h ABPM and biochemical examinations, WCH prevalence was similar to the PAMELA setting. Four BP phenotypes were identified on the basis of office BP and day-time ABPM levels: [1••] normotension (20 %, office BP <120/80 mmHg and day-time ABPM <135/85 mm Hg) [2]; pre-hypertension (25 %, office BP ≥120/80 mmHg but <140/90 mmHg, and normal day-time ABPM) [3]; WCH (12 %, office BP ≥140/90 mmHg and normal ABPM) [4]; sustained hypertension (43 %, elevated office BP and ABPM). Subjects with WCH were older and had a greater body mass index than normotensive and pre-hypertensive ones. Of note, prevalence rates of isolated systolic hypertension was 47 % in WCH and 17 % in sustained hypertensive patients, respectively.

Most of the studies providing epidemiological and clinical data on WCH defined this condition based on a single ABPM recording. Although more reproducible than office BP measurement, 24-h BP monitoring has an intrinsic variability between recording sessions depending on several factors including the degree of physical activity, environmental stimuli, duration and quality of sleep, and seasonal variations. Obviously, this variability affects average ABP levels and the consistency of WCH classification. In this regard, some observational reports where ABPM was performed twice within a few days or weeks interval have shown that WCH is not a stable phenotype in a noticeable fraction of subjects.

In the Hypertension and Ambulatory Recording Venetia Study (HARVEST) Study, 565 grade 1 untreated hypertensive subjects underwent two ABPM recordings within a 3-month interval [12]. According to the results provided by the first ABPM, 90 hypertensive subjects (16 %) were classified as having WCH (mean day-time <130/80 mmHg). After the second ABPM, however, the fraction of WCH fell to 7 %, as only 38 out of 90 subjects confirmed to have this pattern.

We investigated the short-term WCH reproducibility by performing two 24-h ABPMs at 1–4-week interval in untreated hypertensives with a broader range of age and office BP values (40 % with grade 2 hypertension) than the HARVEST study [13]. In approximately 50 % of patients defined as WCH at first ABPM, average day-time values at the following monitoring were >135 mmHg systolic or 85 mmHg diastolic, thus classifying them into the category of sustained hypertensives. In the above-mentioned Spanish ABPM registry, the prevalence of shift from WCH to sustained hypertension observed from the first to the second ABPM (median interval 3 months) was approximately 25 %. On the whole, these findings consistently indicate that WCH diagnosis based on a single ABPM has a short-time limited reproducibility, due to the relevant proportion (25–50 %) of patients moving into the sustained hypertension category at second ABPM.

Accumulating evidence supports the view that WCH subjects are at greater risk of developing sustained hypertension. We addressed this topic in the PAMELA population by identifying individuals with WCH based on in-office and out-of-office (24-h monitoring and home) BP measurements and by detecting new-onset sustained hypertension over a long-term follow-up of 10 years [14••]. The condition of WCH was identified by combined office BP ≥140/90 mmHg and mean 24-h BP <125/79 mmHg or home BP <132/82 mmHg. At baseline, a total amount of 758 (54 %), 225 (16 %), 124 (9 %) and 293 (21 %) participants were classified, respectively, as normotensives, WCHs, masked hypertensives and sustained hypertensives. At second examination 10 years later, 136 previous normotensives (18 %), 95 WCHs (43 %) and 56 masked hypertensives (47 %) had progressed to sustained hypertension. As compared to normotension, the risk of developing sustained hypertension was 2.5-fold higher for WCH (HR 2.51, CI 1.79–3.54, $p < 0.0001$, after adjusting for age and sex). Similar results were obtained when WCH was identified by home BP criteria. Baseline systolic in- and out-of-office BP was the major predictor of progression to sustained hypertension, in addition to the independent although important contribution of age and metabolic variables, i.e. serum glucose and body mass index. Of note, the rise in diastolic BP over-time was more attenuated in WCH subjects, so that pulse pressure increase was even more pronounced. This observation suggests that deterioration of elastic properties of large arteries provides an important contribution to progression to sustained hypertension.

More recently, the risk of progressing from WCH (and masked hypertension) to sustained hypertension has been assessed in a nationwide unselected population sample of 944 Finnic participants [15]. The study evaluated the risk of new-onset sustained hypertension (office BP ≥140/90 mmHg and home BP ≥135/85 mmHg or start of antihypertensive treatment) among 528 normotensives, 142 WCHs, and 63 masked hypertensives at baseline evaluation. During 11-year follow-up, the rate of progression to sustained hypertension gradually increased from normotension (18 %) to WCH (52 %) and masked hypertension (73 %). In WCH subjects, the multivariate-adjusted relative risk for developing sustained hypertension was 2.8 (95 % CI 2.2–3.6, $p < 0.0001$) as compared to normotensive counterparts; this figure is quite close to that previously reported in the PAMELA population.

In the last decades, a large body of evidence has accumulated on the association of WCH with a variety of unhealthy risk factors. Compared to normotensive individuals, WCH subjects have higher serum cholesterol, triglycerides, uric acid and glucose values, increased waist circumference and body mass index I and greater prevalence of metabolic syndrome, all these conditions being associated to an increased cardiovascular risk. It has also been reported that ambulatory (and home) BP mean values, by definition, within the normal range in WCH, are several millimeters of Hg greater than in true normotensives [16]. Metabolic alterations in combination with elevated office BP, high-normal out-of-office BP and increased BP variability contribute to development of subclinical target organ damage at cardiac, vascular and renal level (see next section).

Finally, the risk of progressive impairment of glucose metabolism (i.e. incidence of new-onset glucose intolerance and diabetes mellitus) has been reported to be significantly greater in WCH subjects than in truly normotensives. In the PAMELA population, the increase in plasma glucose levels and incidence of new-onset diabetes (plasma glucose ≥126 mg/dl or use of antidiabetic drugs) among 1412 participants over a 10-year period, was significantly greater in individuals with WCH and masked hypertension than in normotensives (age and sex-adjusted risk 2.9 and 2.7, respectively) and similar to that observed in sustained hypertensives [17•]. In the multivariate analysis, baseline BP values, as well as the use of antihypertensive medications were also found to be independent predictors of glucose alterations, although less relevant than baseline plasma glucose levels and body mass index.

Target Organ Damage and Cardiovascular Prognosis

The benign entity of WCH is still debated [18]. Accumulating evidence focusing on the association of WCH with subclinical

target organ and, more importantly, with incident cardiovascular disease suggests that the risk conveyed by this condition is intermediate between normotension and sustained hypertension. This view, however, is not univocal and is indeed challenged by a series of studies that failed to show significant differences in cardiovascular risk between WCH and normotensive subjects. In this section, before addressing the open question concerning antihypertensive treatment in WCH subjects, we summarize available data on target organ damage and cardiovascular prognosis in WCH.

Over the last few decades, observational and interventional studies have consistently demonstrated that clinical evidence of cardiac and extra-cardiac target organ damage is a powerful, independent predictor of cardiovascular morbidity and mortality, as well as of all-cause death in the general population and in cohorts of patients with systemic hypertension, type 2 diabetes, coronary heart disease, congestive heart failure and chronic renal failure [19–21]. As a consequence, searching for subclinical cardiac and extra-cardiac damage is recommended by current guidelines for refining cardiovascular risk stratification [22].

Cross-sectional studies on the association between WCH and target organ damage have not provided univocal results. Some studies have found an independent association between WCH and left ventricular hypertrophy (LVH), diastolic dysfunction, carotid intima-media (IM) thickening or plaque, renal damage and micro as well as macro-vascular alterations. In contrast, other reports have concluded that in WCH individuals cardiovascular structure and function is not different from truly normotensive subjects after adjusting for confounders, the overall prevalence and magnitude of observed organ damage being predictably less pronounced than those of age- and sex-matched sustained hypertensives. The similarity between the target organ status of WCH and normotension, however, is not in line with the results of two recent meta-analyses. The first meta-analysis compared the extent of structural and functional cardiac damage as assessed by echocardiography in untreated subjects with WCH, as defined by clinic and ABPM, in normotensive and sustained hypertensive subjects [23]. A total of 7382 adult subjects (2493 normotensive, 1705 WCH and 3184 hypertensive individuals) included in 25 studies performed in different clinical settings were considered. The main findings were as follows: (1) LV mass index (LVMI) showed a graded, significant increase from normotensive, WCH to sustained hypertensive subjects; (2) early to late mitral flow ratio (an index of LV distensibility) was significantly reduced in WCH as compared to normotensive subjects and in sustained hypertensives as compared to WCH; (3) left atrial (LA) diameter was greater in WCH as compared to normotensive controls and in sustained hypertensives as compared to WCH; (4) meta-regression analyses demonstrated a direct, significant relation between office systolic BP and LVMI in both WCH and sustained hypertensive subjects, a finding in keeping with the general notion that elevated systolic BP values measured in the office are associated with increased risk of cardiac damage; and (5) the results were unaffected by publication bias and by a single study effect (Fig. 1).

New sophisticated echocardiographic tools such as multilayer and three-dimensional strain analyses have been used to evaluate LV mechanics in WCH. Interestingly, in recent a study by Tadic et al. [24], LV deformation as assessed by new techniques as well as by two-dimensional traditional strain has been shown to be altered in WCH as compared to normotensive subjects. The impaired layer-specific strain demonstrated by this report in the WCH setting reflects the adverse influence of the earliest phases of LV remodelling on LV mechanics.

The second meta-analysis addressed subclinical carotid damage, as assessed by carotid ultrasonography, in untreated WCH [25]. A pooled population of 3478 untreated subjects, 940 normotensive (48 % men), 666 WCH (48 % men) and 1872 hypertensive individuals (57 % men) from 10 studies were analysed. Common carotid intima-media thickness showed a progressive increase of intima-media thickness from normotensive to WCH and hypertensive subjects, the standardized mean being 718, 763 and 817 μm, respectively (Fig. 2). After assessing data for publication bias, only the

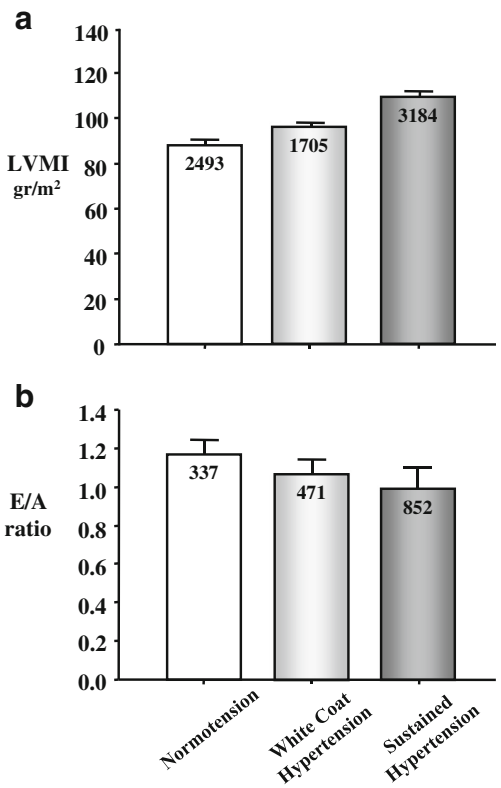

Fig. 1 Left ventricular mass index (LVMI) (**a**) and early-to-late mitral flow velocity ratio E/A ratio (**b**) in normotensive (NT), white coat hypertensive (WCH) and sustained hypertensive (SH) subjects. Meta-analysis from 25 echocardiographic studies. Means ± SE; number of subjects in each group are reported in the histograms. (modified from [23])

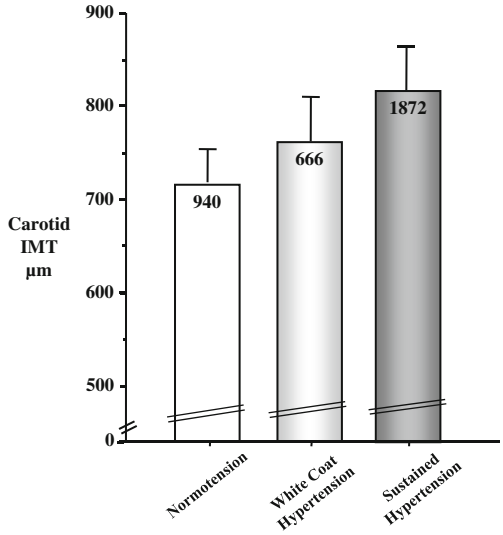

Fig. 2 Common carotid intima-media thickness (IMT) in normotensive (NT), white coat hypertensive (WCH) and sustained hypertensive (SH) subjects. Meta-analysis from 10 ultrasonographic studies. Means ± SE; number of subjects in each group are reported in the histograms. (modified from [25])

difference between normotensive and WCH subjects continued to be significant. These results indicate that carotid damage in WCH is more pronounced that in true normotensive individuals and similar to that of sustained hypertensives.

A recent study by Manios et al. [26], not included in the above-mentioned meta-analysis, added further information to the clinical relevance of WCH by showing that systolic BP is strongly related to carotid intima-media thickness. The authors reported that carotid intima-media thickness in subjects with isolated systolic WCH was significantly higher than in counterparts with isolated diastolic WCH (+52 μm) and not different (+29 μm) from subjects with combined systo-diastolic WCH. This observation is in keeping with the notion that systolic BP compared to diastolic BP has a closer relationship with organ damage and a stronger prognostic value. Less information is available on other measures of organ damage in subjects with WCH vis-à-vis normotensive or sustained hypertensive individuals. However, an increased pulse wave velocity, a greater extent of early renal damage, as assessed by microalbuminuria, and grade 1 and 2 retinopathy have been reported in some studies [27].

In conclusion, when WCH is diagnosed, examinations aimed at assessing subclinical cardiac and vascular damage appear to be desirable in order to provide a comprehensive evaluation of cardiovascular risk related to this condition. This is particularly true when WCH is associated with metabolic alterations, over-weight/obesity and high-normal out-of-office BP levels.

Investigations on the relationship between WCH and cardiovascular outcomes has also produced divergent results, i.e. evidence for an independent association with an increased cardiovascular risk as well as no difference from the association seen for the normotensive status [3, 28–31]. Similar discrepancies have characterized meta-analyses of available studies or of pooled data from a number of cohorts. In a pooled population of 7961 initially untreated subjects (16 % with WCH) who experienced 696 events, Pierdomenico et al. [32] showed that cardiovascular risk was not different in WCH compared to true normotensive subjects (adjusted HR 0.96, 95 % CI 0.65–1.42, $p = 0.85$). Similarly, the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) Study assessed the significance of WCH in 1593 elderly with isolated systolic hypertension, free of cardiovascular disease at baseline and stratified according to the presence or absence of antihypertensive treatment [33]. During a median follow-up of 10.6 years, untreated subjects with WCH (office BP ≥140/<90 mm Hg and ABPM <135/<85 mm Hg) and true normotensives exhibited a similar incidence of non-fatal and fatal cardiovascular events (HR 1.17, 95 % CI 0.87–1.57, $p = 0.29$). Different results, however, have been provided by the International Database of HOme blood pressure in relation to Cardiovascular Outcomes (IDHOCO), a prospective registry totaling 6458 participants from five populations, followed for 8.3 years [34]. Among untreated subjects ($n = 5007$), cardiovascular risk was significantly higher in WCH compared to normotensive subjects (adjusted HR 1.42, 95 % CI 1.06–1.91, $p = 0.02$). Furthermore, a recent meta-analysis by Briasoulis et al. [35•], based on 14 studies with a total number of 29,100 participants (13,538 normotensives, 4806 WCHs and 10,756 sustained hypertensives) showed that incidence of overall cardiovascular events was 6.0 % in WCHs compared to 4.0 % in normotensive subjects, thus meaning a 73 % increased risk ($p < 0.001$). The risk increase was even larger (+179 %, $p < 0.001$) for fatal cardiovascular events, the incidence being 4.0 and 1.2 %, respectively, in the two groups. In WCH individuals, also all-cause mortality risk (+50 %) tended to be greater, although the difference with the normotensive comparators did not achieve statistical significance. The results of this last meta-analysis are in line with those generated by large, carefully designed and high-quality single observational studies such as the PAMELA and DALLAS Heart studies [3, 31].

It worth of comment that inconsistent data provided by the various meta-analyses may be related to the heterogeneity of demographic and clinical characteristics of the pooled populations including the stability of WCH pattern (stable versus unstable) [9, 12, 13].

In this regard, the PAMELA study provided novel findings on the risk of cardiovascular and all-cause mortality assessed over a 16-year follow-up period (the longest follow-up period available in WCH studies) in stable and unstable WCH individuals, (i.e. normal ABPM associated with persistent or non-persistent office BP elevation at two consecutive visits, respectively) [36]. Data were compared with those from a stable true normotensive group (i.e. persistently normal office and

ambulatory BP). Subjects with stable WCH were older, had higher BMI, prevalence of the metabolic syndrome and greater entry LVM index. Compared with the normotensive group, the risk of cardiovascular and all-cause death did not differ in unstable WCH, whereas in stable WCH the risk was increased also after adjusting for baseline confounders, including ABPM (HR 16, $p = 0.001$ for cardiovascular death and 1.92, $p = 0.02$ for all-cause death). These data indicate that only when office BP is persistently elevated, the condition of WCH is associated to an abnormal long-term mortality risk.

The Treatment Dilemma

In the past years, drug treatment was not recommended in WCH subjects, as the protective effect of antihypertensive treatment in this condition was unsettled. This is because, no prospective, randomized trial has ever evaluated whether in this setting administration of BP-lowering drugs leads to a reduction in cardiovascular morbidity and mortality. It should be remarked, however, that a favourable effect of antihypertensive treatment in WCH has been suggested by some intervention studies conducted in middle-aged, elderly and very-elderly hypertensive patients.

In the hypertensive patients enrolled in the European Lacidipine Study on Atherosclerosis (ELSA), office BP and ABP were measured before treatment and at 6-month (office BP) or 12-month (ABP) intervals during the 4-year administration of lacidipine-based or atenolol-based treatment regimen [37•]. The separate analysis of data in patients with sustained hypertension ($n = 1670$) and WCH ($n = 251$) showed that in the former group, office and 24-h mean systolic BP were both markedly reduced throughout the treatment period, the mean change being -20 ± 12 and -10 ± 11 mm Hg, respectively ($p < 0.0001$ for both). In WCH subjects, office BP reduction was almost as marked as in sustained hypertension (-19 ± 11 mmHg; $p < 0.0001$), whereas 24-h systolic BP values showed no substantial fall during treatment. Interestingly, antihypertensive treatment in WCHs induced a marked, progressive attenuation of the difference between office and day-time BP.

A subgroup analysis of the SYSTolic Hypertension in Europe (SYSTEUR) investigated the effect of antihypertensive therapy on clinic and ambulatory BP and the incidence of stroke and cardiovascular events in 695 older patients with sustained and non-sustained systolic hypertension (average day-time BP <140 mmHg) [38]. Active treatment reduced clinic and ambulatory BP in patients with sustained hypertension but only clinic BP in patients with non-sustained hypertension ($p < 0.001$). As compared to placebo group, incidence of stroke and cardiovascular events was lower in both sustained and non-sustained treated hypertensive patients. The favourable effect of active treatment on these outcomes, however, was statistically significant only in patients with sustained hypertension. In the Hypertension in the Very Elderly Trial (HYVET), a double-blind randomized trial of indapamide sustained release 1.5 mg ± perindopril 2 to 4 mg versus matching placebo in hypertensive subjects (systolic blood pressure 160–199 mm Hg) aged >80 years, ABP was measured in 284 participants [39]. During follow-up, the systolic/diastolic BP placebo-active treatment differences averaged 8/5 mmHg for 24-h ABP, and 13/5 mmHg for clinic BP, in line with results of the main study. As 50 % percent of subjects at entry fulfilled the established criteria for WCH, the reduction in total mortality (−21 %) and cardiovascular events (−34 %) observed in the main HYVET study indicates that this condition may benefit from treatment in very elderly.

Office BP reduction in WCH patients documented in the above-mentioned trials has interesting therapeutical perspectives, as persistence of elevated BP values measured in the office has been shown to be associated with increased risk of cardiovascular complications, independently of out-of-office BP. Recently, we ourselves evaluated new-onset LA enlargement (a pivotal marker of cardiac damage) and its correlates over a 10-year period in subjects of the general population enrolled in the PAMELA study [40]. Incidence of LA dilatation similarly increased from the lowest to the highest BP tertile irrespective of whether office, home or 24-h mean values were considered. Notably, office BP turned out to be an independent predictor of LA enlargement in the multivariate analysis, at difference from out-of-office BP. These findings confirm that BP is a major determinants of this marker of cardiac damage and show, for the first time, that out-of-office BP value in predicting the progression of atrial damage is not superior to that of traditional office BP.

Although a growing body of evidence supports the view that WCH is not an entirely benign condition, many arguments against intervention in WCH have been advocated. The most important of them are briefly summarized below.

First, the prognostic value of office BP is less accurate than home and ambulatory BPs. Two major factors have been advocated to explain the limited power of clinic BP in predicting cardiovascular outcomes: (1) poor reproducibility of office BP due to the marked BP variability over time, (2) alarm reaction elicited by the physician triggering transient BP elevations in a noticeable fraction of subjects. Thus, the greater prognostic significance of out-of-office versus office BP represents a reasonable rationale for avoiding the use of antihypertensive drugs in subjects with normal BP out-side medical environment.

Second, WCH is more frequent in mild hypertension and this BP category mostly including subjects at low global cardiovascular risk has not been specifically addressed in clinical trials. The lack of clear-cut benefits of treatment in low-risk subjects with sustained mild hypertension represents a plausible argument against pharmacologic treatment in WCH

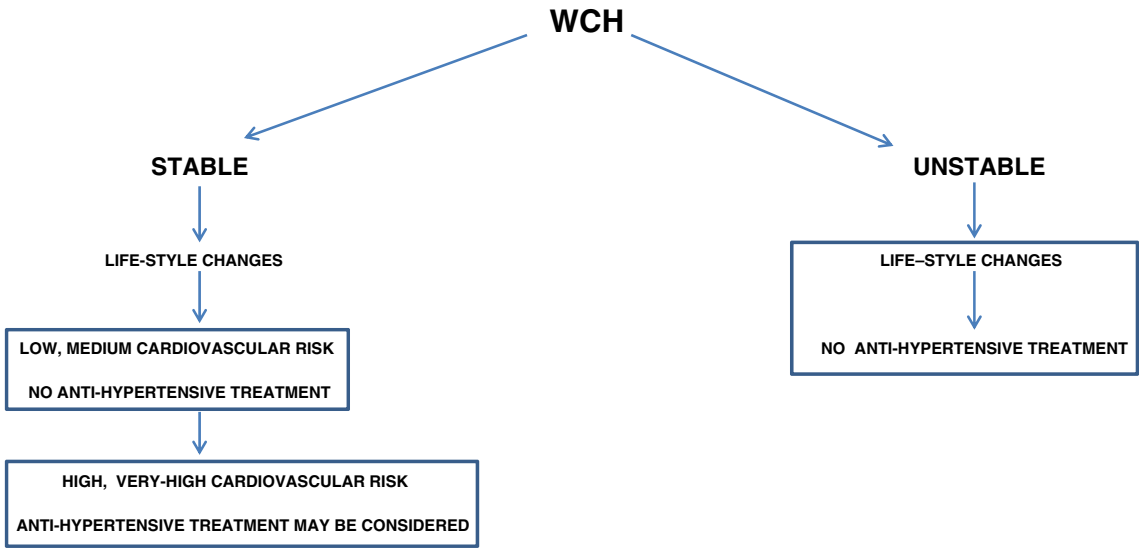

Fig. 3 Flow chart summarizing the therapeutic approach in white coat hypertension (WCH). According to 2013 ESH/ESC guidelines, stratification of total cardiovascular risk is based on four categories: low, moderate, high and very high risk according to systolic BP and diastolic BP and presence of risk factors (RFs), asymptomatic organ damage (OD), diabetes, chronic kidney disease (CKD) stage or symptomatic cardiovascular disease. Subjects with multiple RFs (>3), OD, diabetes and CKD stage 3 are defined at high risk independently of office BP. CKD stage 4 and symptomatic cardiovascular disease are conditions associated to very-high risk. Unstable means non-persistent office BP elevation

subjects at low-medium cardiovascular risk profile. Third, the administration of BP-lowering drugs aimed to reduce office BP in subjects with normal home or ABP may cause excessive BP falls out-side the office environment. In this regard, literature data are scarce and not univocal. Some studies have suggested that active treatment does not significantly lower office and ambulatory BP; on the contrary, other reports showed that antihypertensive treatment induces significant reductions in-office and/or out-of-office BP.

In the last two decades, major international guidelines of hypertension have been recommending that decision making in the hypertension setting should be based not only on BP levels but also on the assessment of global cardiovascular risk. These recommendations have been supported by the notion that only a limited fraction of the hypertensive population is affected by BP elevation alone, a major fraction presenting additional cardiovascular risk factors.

The 2013 European Society of Hypertension and the European Society of Cardiology (ESH/ESC) Guidelines recommend a practical flow chart for estimating the combined effect of risk factors, target organ damage and comorbidities on global risk of cardiovascular events [22]. Estimates take into account office systolic and/or diastolic BP levels, coexistence of modifiable and non-modifiable risk factors, evidence of cardiac and extra-cardiac organ damage, diabetes mellitus and established cardiovascular or renal disease. This method allows to classify hypertensive patients at low, moderate, high and very high risk of 10-year cardiovascular mortality. Starting from this general context, management of WCH subjects should include an accurate evaluation of the global risk. Variables such as hypertension grade, risk factors and associated diseases may be easily assessed by clinical evaluation and routine investigations; detection of target organ damage mostly depends on sensitivity of diagnostic tools.

In WCH subjects without additional cardiovascular risk factors, intervention may be limited to effective lifestyle changes, such as regular aerobic physical activity, weight loss, reduction of salt intake and smoking cessation. This approach has to be associated to a close clinical and laboratory follow-up including regular home BP measurements and periodical ABPM. This is because WCH subjects have an increased risk of developing metabolic abnormalities (i.e. metabolic syndrome or diabetes) and to progress to sustained hypertension. The likelihood of shifting from WCH to sustained hypertension has been shown to be high in subjects with out-of-office BP values in the upper normal range.

In WCH individuals at high- or very-high cardiovascular risk, due to the presence of multiple risk factors, type 2 diabetes mellitus, renal dysfunction, any prognostically validated markers of target organ damage (electrocardiographic or echocardiographic LVH, carotid IM thickening, plaque, microalbuminuria, increased pulse wave velocity) and cardiovascular disease drug treatment may be considered in addition to appropriate lifestyle measures.

Consistent evidence for defining therapeutic strategies in WCH is lacking. General indications of 2013 ESH/ESC guidelines may constitute a road map for treatment of subjects with WCH, taking into account the following considerations. Due the dynamic nature of BP and its marked over-time variability, the first important step is the correct identification of

individuals with stable WCH by repeated office and out-of-office BP measurements. This procedure will allow to identify three main different patterns: (1) "stable" WCH (persistently elevated office and normal out-of-office BP); (2) unstable WCH (non-persistent office BP elevations and normal out-of-office BP); (3) shift from WCH to sustained hypertension. The shift from WCH to the opposite BP pattern (i.e. masked hypertension) appears unlike.

As cardiovascular risk has been shown to be lower in unstable than in stable WCH, antihypertensive treatment is not recommended in the former condition. This is also the case for stable WCH subjects without additional risk factors. Pharmacological treatment may be appropriate in stable WCH with renal dysfunction (microalbuminuria and or e-GFR 30–60 ml/min) and/or type 2 diabetes mellitus, as well as subclinical target organ damage (Fig. 3).

A number of investigations have consistently reported that cardiovascular risk stratification based on routine work-up recommended by guidelines tends to underestimate global risk in a large portion of hypertensive patients. The Assessment of Prognostic Risk Observational Survey (APROS) study [41] included 1074 grade 1 and 2 hypertensive patients classified at low (19 %) or medium risk (81 %) according to routine examinations recommended by World Health Organization/International Society Hypertension guidelines [42]. A marked change in risk stratification was observed when echocardiographic LVH was considered, as more than 36 % of patients previously defined at low-medium absolute risk were reclassified at high risk. The probability of changing the risk class was significantly higher in older than in younger, in grade 2 than grade 1 hypertensives, in hyper- than in normo-cholesterolemic patients. Overall, these findings raise the question whether WCH subjects without any sign of cardiac damage at routine diagnostic work-up (i.e. a normal electrocardiogram) should perform an echocardiogram. This aspect remains a matter of debate because the use of echocardiography for cardiovascular risk stratification in the hypertensive setting is closely dependent on available facilities and financial resources of public healthcare providers.

Untreated WCH is relatively uncommon in the fraction of very-high risk individuals with overt/previous cardiovascular disease. Patients with prior myocardial infarction, cardiac revascularization, angina pectoris and chronic heart failure are usually treated, according to guidelines and good clinical practice, with a variety of medications including angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-antagonists and diuretics.

All major five classes of antihypertensive drugs can be prescribed in stable WCH at high cardiovascular risk, after considering the contraindications in each subject. Low-dose mono-therapy should be the preferred as initial step to minimize the risk of excessive out-of-office BP fall.

Conclusions

A growing body of data show that WCH is by no means a clinically innocent condition because of its frequent association with metabolic alterations, asymptomatic organ damage and risk of cardiovascular events that, although lower than in sustained hypertension, is greater than in truly normotensive individuals. Scanty and contradictory information is available on the response of ABP and office BP to antihypertensive treatment and the cardiovascular protection provided by treatment. Although evidence-based data on therapeutic management of WCH are lacking, the 2013 ESH/ESC guidelines suggest that antihypertensive treatment in WCH should be restricted to high or very-high risk patients. In order to establish the beneficial effects of BP-lowering interventions in WCH, properly designed, randomized outcome-based trials are highly needed.

Compliance with Ethical Standards

Conflict of Interest Drs. Cuspidi, Sala, Grassi and Mancia declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Mancia G, Bertinieri G, Grassi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet. 1983;2:695–8. **The study provides the first description of the alerting reaction induced by the doctor during office BP measurement**.
2. Mancia G, Verdecchia P. Clinical value of ambulatory blood pressure, evidence and limits. Circ Res. 2015;116:1034–45.
3. Mancia G, Facchetti R, Bombelli M, et al. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. Hypertension. 2006;47:846–53.
4. National Institute for Health and Clinical Excellence (NICE). Hypertension. The clinical management of primary hypertension in adults. Clinical (Accessed August 2011 Guideline 127; www.nice.org.uk/guidance/CG127)
5.•• Pickering TG, James GD, Boddie G, et al. How common is white-coat hypertension? JAMA. 1988;259:225–8. **This pioneering paper describes a group of untreated subjects with a persistently elevated office BP but normal ambulatory BP values, defined for the first time as "white coat hypertensives."**.
6. Cuspidi C, Parati G. Isolated clinic hypertension in a general population. J Hypertens. 2006;24:437–40.
7. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension Working Group on Blood Pressure Monitoring.

European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731–68.
8. Omboni S, Aristizabal D, De la sierra A et al. on behalf of ARTEMIS (international Ambulatory blood pressure Registry: TEleMonitoring of hypertension and cardiovascular rISK project) Investigators. Hypertension types defined by clinic and ambulatory blood pressure in 14143 patients referred to hypertension clinics worldwide. Data from the ARTEMIS study. J Hypertens. 2016:34
9. de la Sierra A, Vinyoles E, Banegas JR, et al. Short-term and long-term reproducibility of hypertension phenotypes obtained by office and ambulatory blood pressure measurements. J Clin Hypertens (Greenwich). 2016:1–7.
10. Sega R, Trocino G, Lanzarotti A, et al. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension. Data from the general population (Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study). Circulation. 2001;104:1385–92.
11. Sung SH, Cheng HM, Wang KL, et al. White coat hypertension is more risky than prehypertension: important role of arterial wave reflections. Hypertension. 2013;61:1346–53.
12. Palatini P, Dorigatti F, Roman E, et al. on behalf of the Harvest Study Investigators. White-coat hypertension: a selection bias? J Hypertens. 1998;16:977–84.
13. Cuspidi C, Meani S, Fusi V, et al. How reliable is isolated clinic hypertension defined by a single ambulatory blood pressure monitoring ? J Hypertens. 2007;25:315–20.
14.•• Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension. 2009;54:226–32. **The paper provides evidence of the increased risk of white-coat (and masked) hypertension to develop a sustained hypertension and suggests that these conditions are not innocent from the prognostic point of view**.
15. Sivén SS, Niiranen TJ, Kantola IM, et al. White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-Home study. J Hypertens. 2016;34:54–60.
16. Afsar B. Comparison of demographic, clinical, and laboratory parameters between patients with sustained normotension, white coat hypertension, masked hypertension, and sustained hypertension. J Cardiol. 2013;61:222–6.
17.• Mancia G, Bombelli M, Facchetti R, et al. Increased long-term risk of new-onset diabetes mellitus in white-coat and masked hypertension. J Hypertens. 2009;27:1672–8. **The article shows an increased risk of white-coat and masked hypertension to develop a condition of altered glucose metabolism and suggests the importance of out-of-office blood pressure measurement in the prognostic stratification of hypertensive subjects**.
18. Mancia G. Clinical significance of white-coat hypertension. J Hypertens. 2016;34:623–6.
19. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart study. N Engl J Med. 1990;322:1561–6.
20. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J. 2001;141:334–41.
21. Hald EM, Lijfering WM, Mathiesen EB, Johnsen SH, et al. Carotid atherosclerosis predicts future myocardial infarction but not venous thromboembolism: the Tromso Study. Arterioscler Thromb Vasc Biol. 2014;34:226–3.
22. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of hypertension. J Hypertens. 2013;31:1281–357.
23. Cuspidi C, Rescaldani M, Tadic M, et al. White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. J Hypertens. 2015;33:24–32.
24. Tadic M, Cuspidi C, Ivanovic B, et al. Influence of white-coat hypertension on left ventricular deformation 2- and 3-dimensional speckle tracking study. Hypertension. 2016;67:592–6.
25. Cuspidi C, Sala C, Tadic M, et al. Is white-coat hypertension a risk factor for carotid atherosclerosis? A review and meta-analysis. Blood Press Monit. 2015;20:57–63.
26. Manios E, Michas F, Stamatelopoulos K, et al. White-coat isolated systolic hypertension is a risk factor for carotid atherosclerosis. J Clin Hypertens. (Greenwich). 2016.
27. Wojciechowska W, Stolarz-Skrzypek K, Olszanecka A, et al. Subclinical arterial and cardiac damage in white-coat and masked hypertension. Blood Press. 2016;25:249–56.
28. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension. A 10-year follow-up study. Circulation. 1998;98:1892–7.
29. Strandberg TE, Saloma V. White coat effect: blood pressure and mortality in men: prospective cohort study. Eur Heart J. 2000;21:1714–8.
30. Gustavsen PH, Hoegholm A, Bang LE, et al. White coat hypertension is a cardiovascular risk factor: a 10-year follow-up study. J Hum Hypertens. 2003;17:811–7.
31. Tientcheu D, Ayers C, Das SR, et al. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: analysis from the Dallas Heart Study. J Am Coll Cardiol. 2015;66:2159–69.
32. Pierdomenico SD, Cuccurullo F. Prognostic value of white coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta-analysis. Am J Hypertens. 2011;24:52–8.
33. Franklin SS, Thijs L, Hansen TW, et al. Significance of white coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in relation to Cardiovascular Outcomes Population. Hypertension. 2012;59:564–71.
34. Stergiou GS, Asayama K, Thijs L, et al. International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension. 2014;63:675–82.
35.• Briasoulis A, Androulakis E, Palla M, et al. White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens. 2016;34:593–9. **The article reports the results of a large and up-dated meta-analysis of studies that have addressed the prognostic significance of white coat hypertension**.
36. Mancia G, Facchetti R, Grassi G, et al. Adverse prognostic value of persistent office blood pressure elevation in white coat hypertension. Hypertension. 2015;66:437–44.
37.• Mancia G, Facchetti R, Parati G, Zanchetti A. Effect of long-term antihypertensive treatment on white-coat hypertension. Hypertension. 2014;64:1388–98. **This study shows that a similarly persistent and marked reduction in office BP was induced by treatment in white coat and sustained hypertensives**.
38. Fagard RH, Staessen JA, Thijs L, et al. For the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Circulation. 2000;102:1139–44.
39. Bulpitt CJ, Beckett N, Peters R, et al. Does white coat hypertension require treatment over age 80? results of the Hypertension in the Very Elderly Trial Ambulatory Blood Pressure Side Project. Hypertension. 2013;61:89–94.
40. Bombelli M, Cuspidi C, Facchetti R, et al. New-onset left atrial enlargement in a general population. J Hypertens. 2016;34:1838–45.
41. Cuspidi C, Ambrosioni E, Mancia G, et al. on behalf of the APROS Investigators. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the Assessment of Prognostic Risk Observational Survey. J Hypertens. 2002;20:1307–14.
42. Guidelines Sub committee 1999. World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens. 1999;17:151–83.