White Coat Hypertension

Effect of Long-Term Antihypertensive Treatment on White-Coat Hypertension

Giuseppe Mancia, Rita Facchetti, Gianfranco Parati, Alberto Zanchetti

Abstract—Limited evidence is available on the extent and frequency by which antihypertensive treatment lowers office blood pressure (BP) in white-coat hypertension (WCH). Data are even more scanty and discrepant on the corresponding effect on ambulatory BP (ABP). In the hypertensive patients of the European Lacidipine Study on Atherosclerosis (ELSA), office and ABP were measured before treatment and at 6-month (office BP) or 12-month (ABP) intervals during the 4-year administration of calcium channel blocker–based or β-blocker–based treatment. The two groups were pooled and data were analyzed separately in patients with both office and ABP elevation (n=1670; sustained hypertension) or WCH (n=251; office BP elevation only). In sustained hypertension, office and 24-hour mean systolic BP were both markedly reduced through the treatment period, the mean change being −20.0±12.5 and −10.1±11.0 mmHg, respectively (P<0.0001 for both). In striking contrast, in WCH the office BP reduction was almost as marked as in sustained hypertension (−19.1±11.2 mmHg; P<0.0001), whereas 24-hour systolic BP values showed no fall or a slight progressive significant increase, its mean change during treatment being 1.6±8.6 mmHg (P=0.007). Lowering of office BP occurred at a lower treatment intensity in WCH than in sustained hypertension. Similar findings were obtained for diastolic BP. In WCH, antihypertensive treatment should not be expected to have a lowering effect on ABP, even when office BP undergoes a concomitant marked and persistent reduction. The consequence of this contrasting effect on the incidence of hypertension-related outcomes remains to be established. (Hypertension. 2014;64:1388-1398.) ● Online Data Supplement

Key Words: ambulatory blood pressure monitoring ● antihypertensive agents ● hypertension

A large number of studies has provided information on the clinical characteristics of subjects with isolated office or white-coat hypertension (WCH).1–13 However, information is limited on whether and to what extent WCH is affected by antihypertensive treatment. The limitation includes the effect of treatment on blood pressure (BP) because although some studies have reported that in WCH treatment lowers office BP,14 other studies deny that this occurs, quoting as an example the case of spurious resistant hypertension, that is, a condition in which a normal ambulatory BP (ABP) is accompanied by an office BP that remains elevated despite multiple drug treatment.15,16 Furthermore, the effect of treatment on ABP values of WCH individuals is by no means clear because the reports range from a marked ABP fall to an ABP fall with some drugs only to no ABP fall at all.14,17–27

Previous studies on the BP effects of antihypertensive treatment in WCH have usually assessed ABP by just one 24-hour recording, sometimes without a baseline reference value.14,28 Primary aim of the present study has been to address the issue in a more adequate fashion by taking advantage of the unique data provided by the European Lacidipine Study on Atherosclerosis (ELSA) trial,29 the only prospective antihypertensive treatment trial in which all patients with moderate elevations of both systolic BP (SBP) and diastolic BP (DBP) had office and ABP measured (1) before randomization to treatment and (2) at 6-month (office BP) and 12-month (ABP) intervals during treatment over a follow-up of 4 years. The multiple office and ABP measurements during the treatment period allowed us to more properly address also other issues relevant to WCH, such as the modification with time of the difference between office and ABP, often defined as the WC effect,14,30 and the effect of treatment on within 24 hours and visit-to-visit BP variability (short- and long-term variability) of WCH vis-à-vis sustained hypertensive individuals.31 These issues have never been addressed before.

Methods

Study Design and Patients

The design and methods of the ELSA trial have been described in detail elsewhere.29 Briefly, ELSA was a prospective, randomized, double-blind trial comparing the effects of long-term β-blocker or calcium antagonist treatment on the progression of carotid intima-media thickness in mild-to-moderate essential hypertension. Randomization criteria were (1) an age between 45 and 75 years, assisted patient in a fully supervised setting.24 The two groups were pooled and data were analyzed separately in patients with both office and ABP elevation (n=1670; sustained hypertension) or WCH (n=251; office BP elevation only). In sustained hypertension, office and 24-hour mean systolic BP were both markedly reduced through the treatment period, the mean change being −20.0±12.5 and −10.1±11.0 mmHg, respectively (P<0.0001 for both). In striking contrast, in WCH the office BP reduction was almost as marked as in sustained hypertension (−19.1±11.2 mmHg; P<0.0001), whereas 24-hour systolic BP values showed no fall or a slight progressive significant increase, its mean change during treatment being 1.6±8.6 mmHg (P=0.007). Lowering of office BP occurred at a lower treatment intensity in WCH than in sustained hypertension. Similar findings were obtained for diastolic BP. In WCH, antihypertensive treatment should not be expected to have a lowering effect on ABP, even when office BP undergoes a concomitant marked and persistent reduction. The consequence of this contrasting effect on the incidence of hypertension-related outcomes remains to be established. (Hypertension. 2014;64:1388-1398.) ● Online Data Supplement

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(2) a sitting office DBP between 95 and 115 mm Hg, (3) fasting serum cholesterol, triglyceride, and creatinine levels ≤320, 300, and 1.7 mg/dl, respectively, (4) a readable ultrasound carotid artery scan with an intima-media thickness ≤4 mm, (5) no recent myocardial infarction or stroke, and (6) no insulin-dependent diabetes mellitus.

The included patients were washed from any previous antihypertensive treatment during a period of 4 weeks, after which they were randomized to the assumption of either atenolol or lacidipine, at the morning dose of 50 or 4 mg, respectively. If after 1-month office DBP was not <95 mm Hg, the morning dose was increased (100 mg atenolol and 6 mg lacidipine), with the addition of open label hydrochlorothiazide at 2 progressive doses (12.5 and 25.0 mg, QD) if office BP remained uncontrolled after 2 additional months. Patients and trial personnel were blinded to treatment assignment for the 4 years of the trial.

Office BP measurements

Office BP was measured by a mercury sphygmomanometer at the end of the wash-out period and immediately before randomization (baseline) at monthly intervals during the titration period and at 6-month intervals after the sixth month. The first and fifth Korotkoff sounds were taken to indicate SBP and DBP values, respectively. At each visit, 3 measurements were obtained, with the patient resting in the sitting position for ≥5 minutes. Each BP measurement was followed by a heart rate (HR) measurement via pulse palpation for 30 seconds. The average of the 3 BP or HR values was used as the representative value for the visit.

Ambulatory BP

ABP was measured at baseline and at yearly intervals during treatment within an interval of no more than 1 week from the corresponding office BP measurement. Only validated monitoring devices32 were used, and each patient used the same device throughout the study. The monitoring began in the morning with the inflating cuff positioned around the nondominant arm, and the measuring intervals set at 15-minute intervals during the day (6:00 AM to midnight) and at 20-minute intervals during the night (midnight to 6:00 AM). Patients were instructed to undergo their usual activities during the monitoring period, to keep the arm extended and immobile during the cuff inflations and to come back the following morning for device removal. The recordings were analyzed centrally and considered only if, after removing artifacts according to preselected criteria,33 valid readings were ≥70% of the expected ones (n=92) and ≥1 reading per hour for ≥21 hours was available. In the analyzed study population the number of 24-hour valid BP readings amounted to 87.2% of the expected number of readings at baseline and to 85.8%, 87.7%, 87.6%, and 87.8% from the first to the fourth year of treatment, respectively.

Data Analysis

Patients were divided into 2 groups according to whether at baseline (1) office and ABP were both elevated (sustained hypertension [SH]) or (2) office BP was elevated while ABP was normal (WCH). ABP was regarded as normal if, as indicated by hypertension guidelines, its 24-hour SBP and DBP mean values were <130 and <80 mm Hg, respectively. In each patient calculation was made of the office as well as 24 hours, day and night SBP, DBP, and HR mean values and at various times during treatment, as well as of their changes from baseline. Calculation was extended to the effect of treatment on 24 hours and visit-to-visit SBP and DBP variability. Twenty-four-hour BP variability was measured by the 24-hour coefficient of variation of SBP and DBP (CV, SD multiplied by 100 and divided by the mean value). Visit-to-visit BP variability was assessed by the extent of the on-treatment visit-to-visit BP variations, that is, the CV of the mean SBP or DBP value during the treatment period, separately for office and 24-hour mean SBP and DBP.34 For office BP-only values from the sixth month of treatment onward were used and for ABP-only patients with ≥3 on-treatment 24-hour BP recordings were included. For the group as a whole, the number of visits from which the visit-to-visit CV was calculated was 7.6±1.1 and 3.7±0.5 for office and 24-hour BP, respectively.

Data from atenolol- and lacidipine-treated patients were pooled, averaged for the SH and WCH group, and expressed as means±SD. In addition, the effects of the 2 treatments were also analyzed separately and in either the SH and the WCH groups office and ABP responses to treatment were calculated as a function of the respective baseline BP value, using baseline BP tertiles. Linear correlations were sought between office and ABP at baseline and during treatment and calculations were made of the magnitude of the so-called WC effect,35,36 that is, the difference between office and daytime ABP values before or during treatment. Comparisons between on-treatment and baseline values or between WCH and SH patients were done by, respectively, the paired and unpaired t tests, in either case using the Bonferroni correction for multiple comparisons. The statistical significance of the regression line was established by the Pearson regression coefficient. The slopes of the derived regression lines were compared, whenever indicated, by adding the interaction term (ie, between the SH or WCH group and the independent variable) to the linear model. P values for trend were assessed by linear regression model. A 2-sided P<0.05 was taken as the level of statistical significance.

Results

Baseline Data

A total of 1921 patients met the criteria for data analysis, 251 (13.1%) of whom were defined as WCH. The Table shows that several baseline variables were similar between the 2 groups. There were, however, also some differences such as a higher prevalence of women, a slightly higher age, serum cholesterol, high-density lipoprotein cholesterol and creatinine values and a slightly lower 24-hour HR in the WCH group. As expected, both office and 24-hour SBP and DBP were elevated in SH, whereas in WCH the office SBP and DBP elevation (slightly less pronounced than in SH) was associated with a 24-hour mean BP within the normal range.

Table. Baseline Demographic and Clinical Characteristics of SH and WCH Patients of ELSA

<table>
<thead>
<tr>
<th>Variables</th>
<th>SH</th>
<th>WCH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1670 (86.9%)</td>
<td>251 (13.1%)</td>
<td>...</td>
</tr>
<tr>
<td>Men, %</td>
<td>56.8</td>
<td>32.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>20.7</td>
<td>16</td>
<td>0.082</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.0±7.6</td>
<td>57.1±7.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1±3.6</td>
<td>27.2±4.1</td>
<td>0.48</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>164.5±18.8</td>
<td>159.1±10.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body DBP, mm Hg</td>
<td>101.6±5.3</td>
<td>99.2±4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-hour SBP, mm Hg</td>
<td>144.0±13.0</td>
<td>121.3±6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-hour DBP, mm Hg</td>
<td>90.0±8.2</td>
<td>74.1±4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>76.2±9.3</td>
<td>76.2±8.4</td>
<td>0.79</td>
</tr>
<tr>
<td>24-hour heart rate, bpm</td>
<td>74.4±9.0</td>
<td>72.4±8.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dl</td>
<td>224.9±37.9</td>
<td>230.2±38.8</td>
<td>0.041</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>51.2±14.8</td>
<td>54.3±17.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>132.9±64.3</td>
<td>133.1±63.8</td>
<td>0.97</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.96±0.19</td>
<td>0.93±0.19</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>4.0</td>
<td>4.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>29.4</td>
<td>30.8</td>
<td>0.87</td>
</tr>
<tr>
<td>Atenolol use, %</td>
<td>50.4</td>
<td>47.8</td>
<td>0.45</td>
</tr>
</tbody>
</table>

The symbol ± refers to the SD of the mean. DBP indicates diastolic blood pressure; ELSA, European Lacidipine Study on Atherosclerosis; HDL, high-density lipoprotein; SBP, systolic blood pressure; SH, sustained hypertension; and WCH, white-coat hypertension.
Effects of Treatment on Office and ABP

Treatment was less intense in WCH than in SH patients, the 4 treatment steps being adopted in 67.7%, 12.3%, 12.8%, and 7.3% patients of the former versus 42.9%, 16.1%, 17.7%, and 23.2% patients of the latter group, respectively. Figure 1 shows that treatment was associated with an early, marked, and persistent reduction of office SBP and DBP. This was the case in both SH and WCH, although from the second month onward the SBP reduction was slightly (even if usually significantly) greater in SH than in WCH patients, possibly because of a more frequent increment along treatment steps in SH than in WCH. Similar observations were made when data were separately analyzed for lacidipine and atenolol treatment (Table S1 in the online-only Data Supplement).

As shown in Figure 2, in striking contrast with the similar office BP reduction, 24-hour mean SBP and DBP were persistently and significantly reduced only in SH although to a definitely smaller extent than office SBP/DBP ($P$ always $<0.0001$). In WCH treatment did not lower 24-hour mean SBP and DBP, which rather exhibited a small but significant progressive increase. Similar observations were made when mean day and night SBP and DBP values were considered (Figure 3) as well as when data were separately analyzed for patients under lacidipine or atenolol treatment (Table S1).

In all subjects pooled, treatment was associated with a persistent reduction of office and 24-hour mean HR values, the latter being significantly greater in SH than in WCH individuals (Figure S1). The bradycardic effect was only visible in the group under atenolol treatment (Table S1).

Office Versus ABP Values and Changes (All Patients Pooled)

Figure 4 (upper) shows that in SH the treatment-induced office or 24-hour mean SBP reduction was progressively greater from the tertile with the lowest to the tertile with the highest baseline SBP value ($P$ for trend $<0.0001$ for both). However, in WC hypertensives a progressively greater SBP reduction with an increasing SBP baseline value was seen for office SBP ($P$ for trend $<0.0001$), whereas 24-hour mean SBP remained substantially
unchanged in the 2 upper tertiles of baseline SBP values and significantly increased in the lowest one. Similar findings were obtained for office and ambulatory DBP (Figure 4, lower).

As shown in Figure 5 (left), in SH, 24-hour mean SBP correlated with office SBP values so that both before and during treatment progressively lower values of one pressure were associated with progressively lower values of the other. In striking contrast, in WCH, 24-hour mean SBP values were all in a narrow range, independently of the level of office SBP, and the regression curve was markedly flatter than that calculated in SH (P for the difference in the 2 regression lines <0.001). In both SH and WCH patients, 24-hour SBP was always lower than office SBP, the 2 values becoming progressively closer as SBP became less and the difference disappearing (crossing of the identity line) at about 130 to 120 mm Hg office SBP. Similar observations were made for DBP, which showed no difference between office and 24-hour mean values at ≈70 mm Hg (Figure 5, right).

Treatment and WC Effect

Treatment 6 shows that at baseline the office-daytime SBP and DBP differences were (1) greater in WCH than in SH and (2) in either group the difference underwent a marked reduction at the first year of treatment, with a subsequent much more modest progressive fall. As shown in Figure 7, both at baseline and during treatment the WC effect showed a close relationship with office SBP and DBP values. In the absence of treatment the relationships were much steeper for WCH than for SH individuals (slope difference significant at P<0.0001). However, although in SH treatment did not significantly modify the WC effect–office BP relationships (P value for slope difference 0.70 and 0.17 for SBP and DBP, respectively), the steepness of the relationship was markedly flattened by treatment in WCH (slope difference significant at P=0.024 for SBP and 0.002 for DBP) meaning that differences in WC effect between WCH and SH were made smaller by treatment. Both at baseline and during treatment differences in WC effect between the 2 groups of patients tended to disappear at office BP values of ≈110/70 mm Hg.

BP Variability in SH and WCH Before and During Treatment

Figure 8 shows that before treatment 24-hour SBP and DBP CV (short-term variability) were significantly higher in WCH than
in SH (24-hour SBP CV +11.9%; 24-hour DBP CV +16.7%; \( P<0.0001 \) for both). In SH, 24-hour SBP and ABP CV were not consistently or only minimally affected by treatment. By contrast, in WCH, SBP and DBP CV were significantly reduced throughout the treatment period, although remaining until the end somewhat greater than the corresponding SH values.

On-treatment visit-to-visit office BP variability (long-term variability) was not significantly different between SH and WCH patients (SBP CV: 6.2±2.8% and 5.9±2.4%; DBP CV: 6.1 and 5.8, respectively). This was the case also for on-treatment visit-to-visit 24-hour BP variability, which was smaller than the corresponding office value, but again not significantly different in the SH and WCH groups (SBP CV: 4.8±2.7% and 4.5±2.2%; DBP CV: 5.0±2.8% and 5.2±3.0%, respectively).

### Discussion

The major finding of these analyses of ELSA data is that in WCH antihypertensive treatment reduced office BP to a degree that was, quantitatively similar to, or only slightly less pronounced than that seen in SH, whereas it did not have any consistent lowering effect on 24 hours, daytime and nighttime BP, at variance with the clearcut persistent reduction seen in the SH group. This is an observation that could not be made in previous analyses of other interventional trials, because only in ELSA ABP was systematically measured before treatment and repeatedly during several years of treatment, whereas in most other studies ABP monitoring was limited to a relatively small subgroup of patients or done during treatment only.
As to the effects of treatment on office BP, our data were derived from a controlled trial, with treatment steps determined by protocol according to the achieved DBP. This makes it possible for our analysis to provide the additional information that in WCH patients office BP is not only markedly reduced by antihypertensive treatment but also more easily reduced than in SH, because 3 of 4 WCH patients achieved target BP with low-dose monotherapies, whereas this occurred in <2 of 4 patients among SH. This indicates that in WCH office BP is susceptible to therapy, which can in ≈75% of the cases bring BP down to target values without the need of resorting to combination of ≥2 antihypertensive drugs.

The data provided by the present study raise the question of the reason for the absence of an ABP lowering effect of treatment in WCH. The most obvious explanation is that, as also shown in our patients by the tertiles data, not only office but also ABP reductions are proportional to baseline BP values, which means that little BP lowering effect can be expected when, as in WCH, the initial ABP is normal or low. However, in other antihypertensive treatment studies, ABP has been reduced below the baseline values exhibited by the WCH patients of the present study, and we have thus to consider the possibility that the easy response of office BP to treatment that characterized WCH prevented lower ABP values from being achieved. Furthermore, in our WCH patients, ABP often showed not just no change but an increase, which was consistent in patients with baseline ABP in the lowest tertile. This can be explained by the continuous analysis of Figure 7, showing that in WCH individuals the lowest on-treatment BP values are found around the point where ABP becomes higher than office BP. However, because the ELSA trial lasted ≈4 years it cannot be excluded that the WCH patients had some time-related trend to BP increase, only partly contrasted by the lower treatment intensity these patients received. This explanation is compatible with the observation that, compared with true normotensive individuals, WC hypertensive subjects exhibit a more pronounced long-term increase in 24-hour ABP, with an almost two and a half greater risk of developing SH >10 years.9

In our WCH patients antihypertensive treatment was accompanied by a marked progressive attenuation of the difference between office and daytime BP. However, the reduction was marked, progressive, and in percentage not smaller also in SH, indicating that the consequence of treatment on the so-called WC effect is not substantially different in the 2 groups.
addition, our detailed analyses of the relationship between the office–daytime BP difference and office BP before and during treatment provide some insight on the unresolved issue of the real nature of this phenomenon, given that its ability to precisely reflect the alarm-elicited BP rise to the doctor’s visit has been questioned.\textsuperscript{31,40} The ELSA data confirm older findings

**Figure 5.** Correlation between office systolic blood pressure (SBP) and 24-hour mean SBP and office diastolic blood pressure (DBP) and 24-hour mean DBP in individual patients at baseline and during treatment. Data are shown separately for sustained hypertension (SH) and white-coat hypertension (WCH). SBP changes during the treatment period were averaged. Significance of the regression equations is indicated after each equation. Significance of the difference in the slope of the regressions between WCH and SH is indicated between the right end of the regression lines.

**Figure 6.** Upper The office–daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) differences at baseline (B) and during treatment in white-coat hypertension (WCH; white square and histogram) and sustained hypertension (SH; black square and histogram). Lower, The percent reductions (from B) during treatment. Data are shown as mean±SD for the 2 treatment groups pooled. †Statistical significance (P<0.0001) of the change from B. Symbols as in the preceding figures and the Table.
that the WC effect is progressively lower the lower office BP is, as well as the results of a recent study of normotensive and hypertensive children and adolescents showing the WC effect disappears and changes sign (ABP higher than office BP) at office BP values <110 to 120/65 to 70 mm Hg. They also provide, however, additional information that previous studies, being noninterventional, could not provide. In the absence of treatment the relationship of the WC effect to office BP was much steeper in WCH than in SH individuals, and only the WCH curve steepness was reduced by treatment, whereas the SH curve steepness remained substantially unmodified. Consistently with these observations, 24-hour SBP and DBP variabilities were significantly higher in WCH than in SH, and treatment affected 24-hour variabilities only in WCH, thus markedly reducing differences between the 2 populations of patients. These findings suggest the so-called WC effect may be related to BP variability and that its extent may largely depend on regression to the mean. Lack of separation of the WC effects between WCH and SH individuals both before and during treatment (Figure 7) further suggests that the so-called WCH individuals are simply those whose WC effects are on the upper end of the distribution curves at each office BP values. The nature of the WC effect, therefore, remains largely undetermined and, despite its attractiveness, the term commonly used conveys the incorrect information that we know of this phenomenon more than we actually do.

Our analysis of the ELSA data raises another question of practical importance, ie, whether failure of antihypertensive treatment to lower ABP means that in WCH little or no cardiovascular protective effects of BP lowering interventions should be expected. This conclusion has been drawn from the results of a large database, in which patients under antihypertensive treatment who exhibited an elevation of office but not of ABP had the same cardiovascular risk of untreated normotensive individuals. It is also supported by a post hoc analysis of a subgroup of patients from the Systolic Hypertension in Europe (SystEur) trial, which showed that in WCH antihypertensive treatment did not lower cardiovascular events significantly more than in the placebo group, at variance with the protective effect seen in patients with SH. However, several considerations weaken these conclusions. First, in the SystEur substudy, the number of patients and events was too small to give the results sufficient statistical power. Second, in both the SystEur and the previously mentioned large databases, only 1 on-treatment ABP was available, which may have interfered with an accurate estimate of the prevailing daily life BP values achieved with the treatment regimen. Third, in the large database, there are no ABP baseline data, and thus there is no possibility to exclude that WCH individuals had originally a higher ABP, with a higher CV risk that was beneficially affected by treatment. Finally, (1) office BP reductions have been shown to be predictive of the achieved benefit in a

Figure 7. Correlation between the office–daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) differences and office BP values at baseline and during treatment in individuals with white-coat hypertension (WCH) and sustained hypertension (SH). On-treatment data were averaged. Significance of the regression equations is indicated after each equation. Significance of difference between slopes of the regression in WCH and SH is indicated between the right end of the regression lines.
large number of trials,\textsuperscript{43,44} including those on mild hypertension,\textsuperscript{45–48} when WCH prevalence can be as high as 40% of the trial population,\textsuperscript{10,34,49} (2) when properly measured, office BP values have been found to correlate with organ damage or predict outcome not less or only slightly less than ABP.\textsuperscript{40,51} This has been shown to occur also in the ELSA patients,\textsuperscript{52} in whom clinic BP and 24-hour BP were found to be both strong predictors of cardiovascular events (odds ratios 1.03 versus 1.04 per mm Hg, SBP increase, respectively); and (3) office BP values have also been found to independently predict the increased risk of developing SH in individuals with either WCH or a metabolic syndrome.\textsuperscript{5,53} Taken together these data indicate that the possibility that in WCH a treatment-induced reduction of the office BP translates into a protective effect even in the absence of an ABP reduction cannot be ruled out.

Two further results of our study are worth being mentioned. One, WCH accounted for only 13.1% of the ELSA hypertensive population, a figure much lower than that reported in other studies.\textsuperscript{10,34,54} This can be explained by the fact that the prevalence of WCH bears a steep inverse relationship with the magnitude of the office BP elevation, with a much lower prevalence when, as in the ELSA and other trials, only patients with office hypertension above a given cutoff are recruited.\textsuperscript{10,29,55} Two, although visit-to-visit BP variability during treatment did not consistently differ between WCH and SH, within 24-hour or short-term BP variability did not change with treatment in the SH group, whereas exhibiting a higher pretreatment value and a consistent on-treatment reduction in the WCH one. Because 24-hour BP variability is an independent predictor of cardiovascular morbidity and mortality,\textsuperscript{1,36–38} this may be taken as another finding potentially in favor of the protective effects of treatment in this condition.

### Perspectives

WCH, that is, a condition in which office BP is elevated while ABP is normal, is common and recent data show that it is by no means clinically innocent because of its frequent association with metabolic abnormalities, subclinical organ damage, and a risk of CV events that, although less than in SH, is greater than that of truly normotensive subjects. Information is limited and contradictory, however, on how ABP and office BP respond to antihypertensive treatment and thus whether its effect leads to CV protection. In the present analysis of the ELSA (the only available trial in which all hypertensive patients underwent office and ABP measurements before and at yearly intervals during a 4-year treatment period), WCH and SH showed a similarly persistent and marked reduction in office BP. However, although in SH the office BP reduction was accompanied by a persistent marked reduction of 24 hours, daytime and nighttime BP, in WCH ABP did not show a reduction but rather a small progressive increase. Whether absence of any daily life BP reduction implies that in WCH no benefit should be expected by BP lowering interventions will have to be established by randomized outcome-based trials. Given the high prevalence of WCH (up to 30%–40% of the hypertensive individuals) this will be of major importance for public health.

### Disclosures

G. Mancia, G. Parati, and A. Zanchetti have received honoraria as lecturers/chairmen at national and international meetings from the main drug companies in the cardiovascular area. The other author reports no conflicts.

### References


Effect of Long-Term Antihypertensive Treatment on White-Coat Hypertension
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EFFECT OF LONG-TERM ANTIHYPERTENSIVE TREATMENT ON WHITE COAT HYPERTENSION.

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Running title: Treatment of white coat hypertension.

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Table S1  SBP, DBP and HR changes induced by Lacidipine-based and Atenolol-based treatment in sustained hypertension (SH) and white coat hypertension (WCH).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lacidipine</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Office</td>
<td>24h</td>
</tr>
<tr>
<td></td>
<td>SH (n=841)</td>
<td>WCH (n=120)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-20.3±11.7*</td>
<td>-20.4±11.3*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-13.9±6.2*</td>
<td>-14.8±5.3*</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>0.34±8.7</td>
<td>-0.44±8.3</td>
</tr>
</tbody>
</table>

Data are shown as means ± standard deviation of all data during the treatment period. SBP: systolic blood pressure; DBP: diastolic BP; HR: heart rate. *p<0.001 and †p<0.05 vs baseline values.
Office and 24h mean heart rate (HR) changes during the 4-year treatment period in SH and WCH. Data from all subjects pooled. Explanations and symbols as in Figures 1 and 2.
白大衣高血压（摘要）

白大衣高血压的长期降压治疗效果

Effect of Long-Term Antihypertensive Treatment on White-Coat Hypertension

Giuseppe Mancia, Rita Facchetti, Gianfranco Parati, Alberto Zanchetti

张抒扬 译

在白大衣高血压（white-coat hypertension，WCP）的门诊降压治疗中，关于诊室血压的降低程度和测量频率的数据非常有限，同时门诊降压治疗对动态血压（ambulatory blood pressure，ABP）影响的数据更少而且差异较大。在欧洲拉西地平抗动脉粥样硬化的研究（European Lacidipine Study on Atherosclerosis，ELSA）的高血压患者中，有以钙通道阻滞剂为基础用药或以β受体阻滞剂为基础用药的降压治疗方案，在用药前分别测量他们的诊室血压和动态血压。在用药后的4年间，每隔6个月记录一次诊室血压，每隔12个月记录一次动态血压，最后将两种降压方案的数据混合汇总分析，发现用药前诊室血压和动态血压均高的有1670例（持续性高血压），诊室血压高而动态血压不高的有251例（白大衣高血压）。持续性高血压人群经过治疗后，其诊室血压和动态血压分别降低20.0 ± 12.5 mm Hg（P<0.0001）和10.1 ± 11.0 mm Hg（P<0.0001）；而白大衣高血压经过治疗后其诊室血压降低19.1 ± 11.2 mm Hg（P<0.0001），但动态血压显示24小时收缩压不但没有降低反而升高1.6 ± 8.6 mm Hg（P=0.007）。比较降低诊室血压所需要的治疗强度，白大衣高血压要低于持续性高血压。舒张压的数据分析也有类似的结果。因此在白大衣高血压的降压治疗中，即使诊室血压有显著和持续的降低，也不应该期待动态血压有明显的降低。这种相反的结果，与高血压相关事件发生率之间的关系仍然有待确定。(Hypertension. 2014;64:1388-1390)

流行病学人群（摘要）

设定动脉血压监测不同间隔阈值对人群中白大衣和隐蔽性高血压风险评估的影响

Setting Thresholds to Varying Blood Pressure Monitoring Intervals Differentially Affects Risk Estimates Associated With White-Coat and Masked Hypertension in the Population

Kyoko Nomura, Takayoshi Ohkubo, Jorgen Jepsen, Christian Torp-Pedersen, Eamon Dolan, Katarzyna Stolarz-Skrzyniek, Sofia Malyutina, Edoard Casiglia, Yuri Nikitin, Lars Lind, Leonilda Luczardo, Kalina Kawecka-Jaszcz, Edgardo Sandoya, Jan Filipovsky, Gladys E. Maestre, Jiguang Wang, Yutaka Imai, Stanley S. Franklin, Eoin O’Brien, Jan A. Staessen, on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators

姜一农 译

对于诊断白大衣高血压和隐蔽性高血压的动脉血压监测中的时间段，还缺乏以结果为导向的建议。我们交叉分类了8237名参与12项研究的未经治疗的参与者（平均年龄50.7岁；48.4%女性），使用≥140/≥90，≥130/≥80，≥135/≥85和≥120/≥70 mm Hg分别作为传统、24小时、白天和夜间的血压阈值。白大衣高血压是在传统测量中血压高于但动态血压正常，隐蔽性高血压则相反。分类参与者的时段是白天、夜间和24小时，其单独考虑，再考虑24小时加白天或加夜间或加者。根据所选中的时间段，白大衣和隐蔽性高血压率分别是6.3%-12.5%和6.4%-16.6%。在91 046人年中，729名参与者发生过心血管事件。在多变量分析中，以全年中所有时间段的正常血压作为参考，如果仅考虑白天（1.38；P=0.03），仅考虑夜间（1.43；P=0.0074），仅考虑24小时（1.24；P=0.20），24小时+白天（1.24；P=0.18），24小时+夜间（1.15；P=0.39），24小时+白天+夜间（1.16；P=0.41），白大衣高血压的危险比（hazard ratio）逐渐下降。与正常血压相比，隐蔽性高血压的危险比都有显著性（P<0.0001），范围：1.76-2.03。总之，识别真正的低风险白大衣高血压需要同时设定24小时、白天和夜间的血压阈值。尽管任何时间段都足以诊断隐蔽性高血压，但是目前的指南仍推荐在临床上实际记录完整的24小时血压。(Hypertension. 2014;64:935-942)